INFLUENCE OF BETA BLOCKERS ON COMPLICATIONS OF CIRRHOSIS

DISSERTATION SUBMITTED FOR

DM MEDICAL GASTROENTEROLOGY

BRANCH –IV

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CERTIFICATE

This is to certify that this dissertation entitled **"Influence of Beta Blockers on Complications of Cirrhosis"** submitted by **Dr. Kayalvizhi J** to the Faculty of Medical Gastroenterology, the Tamilnadu Dr. MGR Medical University, Guindy, Chennai – 600032, in partial fulfillment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by her under my direct supervision and guidance, during the academic year 2014 -2017.

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DECLARATION

I **Dr. Kayalvizhi J** declare that I carried out this work on **"Influence of Beta Blockers on Complications of Cirrhosis"** at the department of Medical Gastroenterology, Government Peripheral Hospital and Kilpauk Medical College. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, and diploma to any university, board either in India or abroad.

This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the D.M. Degree examination in Medical Gastroenterology.

Kilpauk Medical College **Dr. Kayalvizhi J**

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INTRODUCTION

Histologically cirrhosis, a chronic liver disease is characterized by fibrosis and the alteration of normal liver architecture into abnormal nodules. In the west, it is the leading cause of mortality, particularly affecting the productive age population. In our country, an estimated 188,575 cirrhosis related death in 2010[1] which is 18.3 % of the universal burden of the disease. And the deaths due to cirrhosis increased globally from 2005 to 2015, whereas age-standardized cirrhosis mortality rates fell during the same period [2]. The economic burden, the disease poses on the family of the patient and the patient's loss of productive life has been overseen largely. The complications of cirrhosis are protean including portal hypertension, ascites, hepatorenal syndrome, hepatic encephalopathy, portal vein thrombosis, hepatocellular carcinoma and eventually death. Besides the complications that are disease driven, certain complications are worsened by the therapies instituted for the management of cirrhosis, of which beta blockers which have been used for managing portal hypertension since the 1980s when Lebrec [3] et al first demontsrated the usefulness of non selective beta blockers in a randomized controlled trial involving 74 patients with variceal bleeding, has recently drawn the interest of researchers and hepatologists worldwide, when concerns of its safety in advanced cirrhosis was raised by Serste[4].

REVIEW OF LITERATURE

Cirrhosis is a final pathway for a wide variety of liver diseases. The rate at which the disease worsens from a state of chronic liver disease to cirrhosis varies according to the etiology. It could be weeks in complete biliary obstruction to decades in case of chronic viral hepatitis C. Whatever maybe the cause, the hepatic insult activates profibrogenic mechanisms which leads to progressive accumulation of fibrillar extracellular matrix [25,26,27]. The eventual fibrosis leads to rise in intrahepatic resistance, which leads to increase in portal and hepatic arterial blood flow thereby resulting in portal hypertension.

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION:

The hepatic venous pressure gradient (HVPG) of a value greater than 5 mm of Hg, defines portal hypertension and is perhaps the most reliable prognostic indicator of the formation of varcies and ascites [30]. Hepatic architectural distortion leads to increased intrahepatic vascular resistance. Also contributing to these are, endothelial dysfunction, intrahepatic vasoconstriction and intrahepatic vascular shunts between the afferent and efferent vessels of the organ[28, 29]. (Fig 1)The splanchnic vessels dilate in response to a relatively underperfused liver or extrahepatic excess of NO, with sGC-PKG signalling and smooth muscle cell relaxation [32]. This leads to increased portal blood flow, which maintains portal hypertension. These hemodynamic changes lead to the hyper dynamic circulation, which manifests as high cardiac output with low systematic vascular resistance and arterial hypotension [31]. The splanchnic vasodialtaion and the imbalance between vasoconstrictors and vasodilators are amenable to drug therapy.

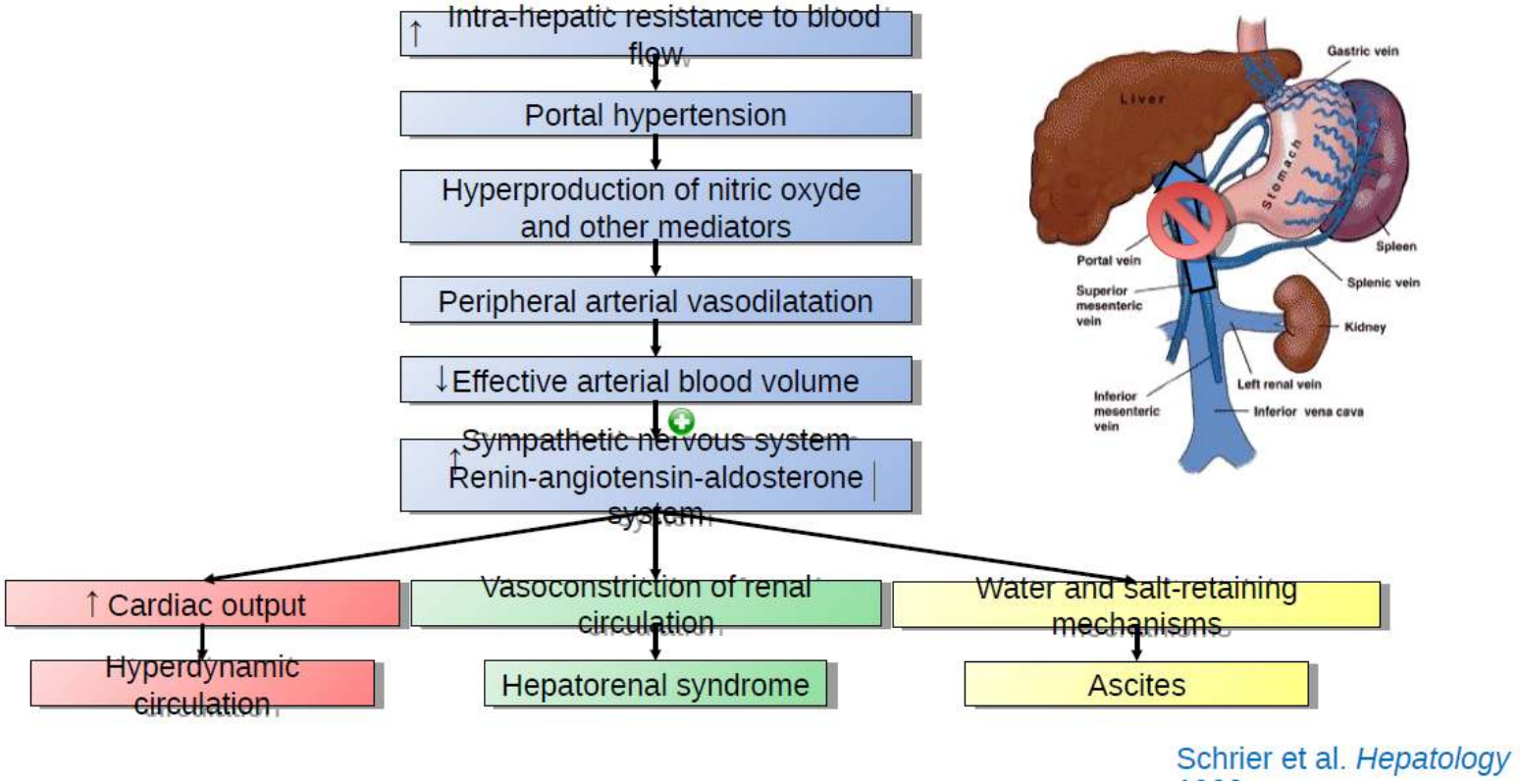


Figure 1: Pathological mechnanisms involved in portal hypertension

PHARMACOLOGICAL ACTION OF BETA BLOCKERS

Non -selective beta-blockers (NSBB) exert their effects in two main ways to reduce the portal pressure. (Fig2).

1. Firstly, there is beta 1 receptor blockade, which results in reduced cardiac output and splanchnic blood flow [22].

2. Secondly, beta 2 receptor blockade results in splanchnic vasoconstriction caused by unopposed effect of alpha 1 receptors [23].

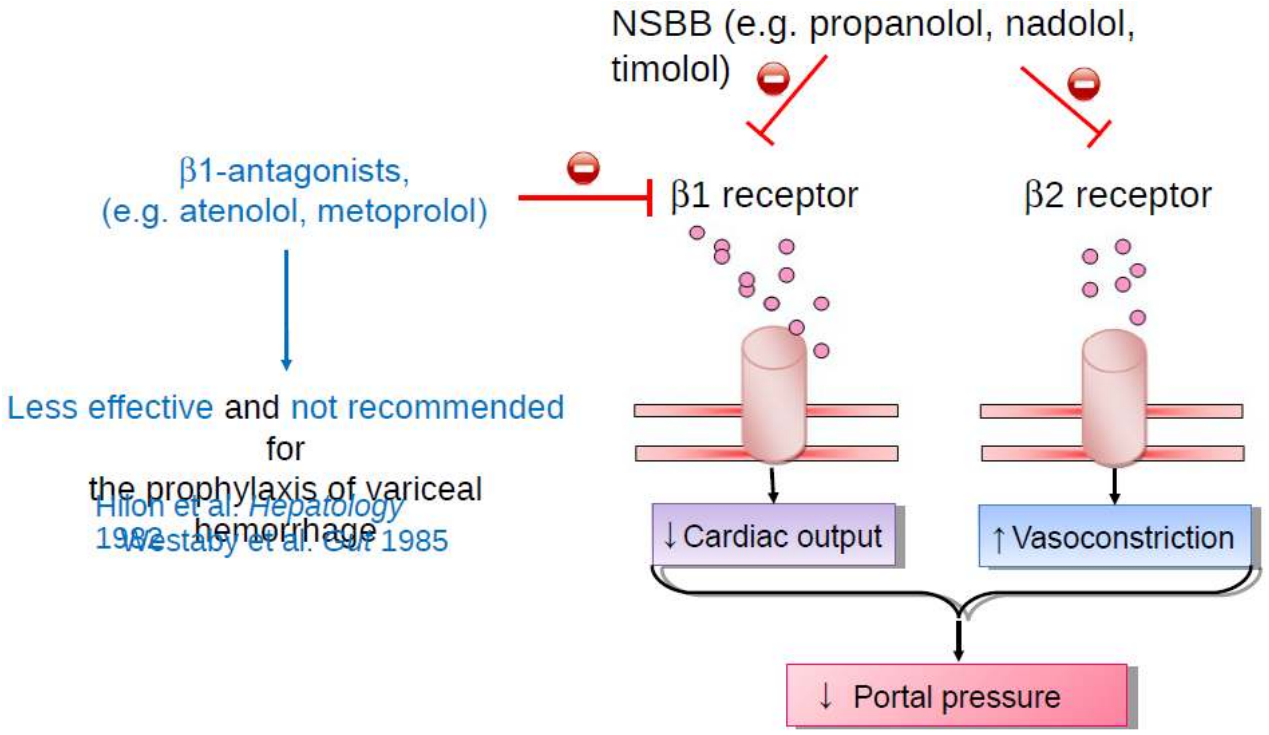


Figure 2: Mechanism of action of non selective beta blockers

Strikingly the effects of beta 2 blockade occur only after chronic use [34]. The response to propranolol therapy as measured by HVPG is variable, with some studies reporting to 31 %. (Table 1). Of note, one - third of patients do not have a hemodynamic response to propranolol, inspite of studying blood flow patterns in azygous system, pointing that all patients may have a reduction in portocollateral flow [35]. In an observational study [36], there was significant difference between the acute and chronic effect on HVPG. In those who had poor chronic response, they demonstrated increased resistance to portal blood flow. Patients with hypertension exhibit a similar response to propranolol as those who are normotensive, with a reduction in mean arterial pressure only seen in hypertensive patients [37]. Therefore, NSBB are a good choice in hypertensive patients with cirrhosis. Nadolol has a longer half-life than propranolol as a result of low lipid solubility and hepatic metabolism [38]. This permits once-daily dosage. Hemodynamic effects mirror those of propranolol, although effects on mean arterial pressure may not be so pronounced [33].

BETA-BLOCKERS USED IN PORTAL HYPERTENSION AND THE PRINCIPLE HEMODYNAMIC EFFECTS IN CLINICAL STUDIES

		Effects on hemodynamic parameters (% decrease from baseline)					
Drug	Mechanism of action	Mean arterial pressure	Cardiac output/cardiac index	Hepatic venous pressure gradient	Estimated hepatic blood flow	Azygous blood flow	Clinical studies
Propranolol	Non-selective beta-blocker	0–14	10–31	10–31	0–39	29–47	Phase III
Nadolol	Non-selective beta-blocker	0–6	25–29	19–32	10–24	N/A	Phase III
Timolol	Non-selective beta-blocker	NS	N/A	20	N/A	N/A	Phase III
Atenolol	Selective beta 1 receptor blocker	NS	32	NS	N/A	N/A	Phase II
Metoprolol	Selective beta 1 receptor blocker	N/A	17	19–22	NS	N/A	Phase III
ICI 118551	Selective beta 2 receptor blocker	NS	14	11	N/A	N/A	Phase II
Mepindolol							
Carvedilol	Non-selective beta-blocker and alpha 1 receptor blocker	4–17	7–18	15–43	10–65	14–20	Phase III

Table 1: Effects of hemodynamic parameters

N/A, data unavailable; NS, not significant compared to baseline.

The most commonly followed algorithms are the AASLD and the BAVENO VI guidelines for management of portal hypertension and varices. According to the latest AASLD guidelines in 2016 for portal hypertension, those who have compensated cirrhosis with mild portal hypertension / clinically significant portal hypertension without any gastroesophageal varices, beta blockers are not recommended as they are ineffective at this stage and treatment of the underlying disease alone is sufficient. In patients who have gastroesophageal varices and or bled previously, either primary prophylaxis with EVL or NSBB or secondary prophylaxis with the same is recommended depending on the size of the varices. In our department, we follow the EASL guidelines for starting the patient on beta blocker therapy which is as follows.(Fig 3)

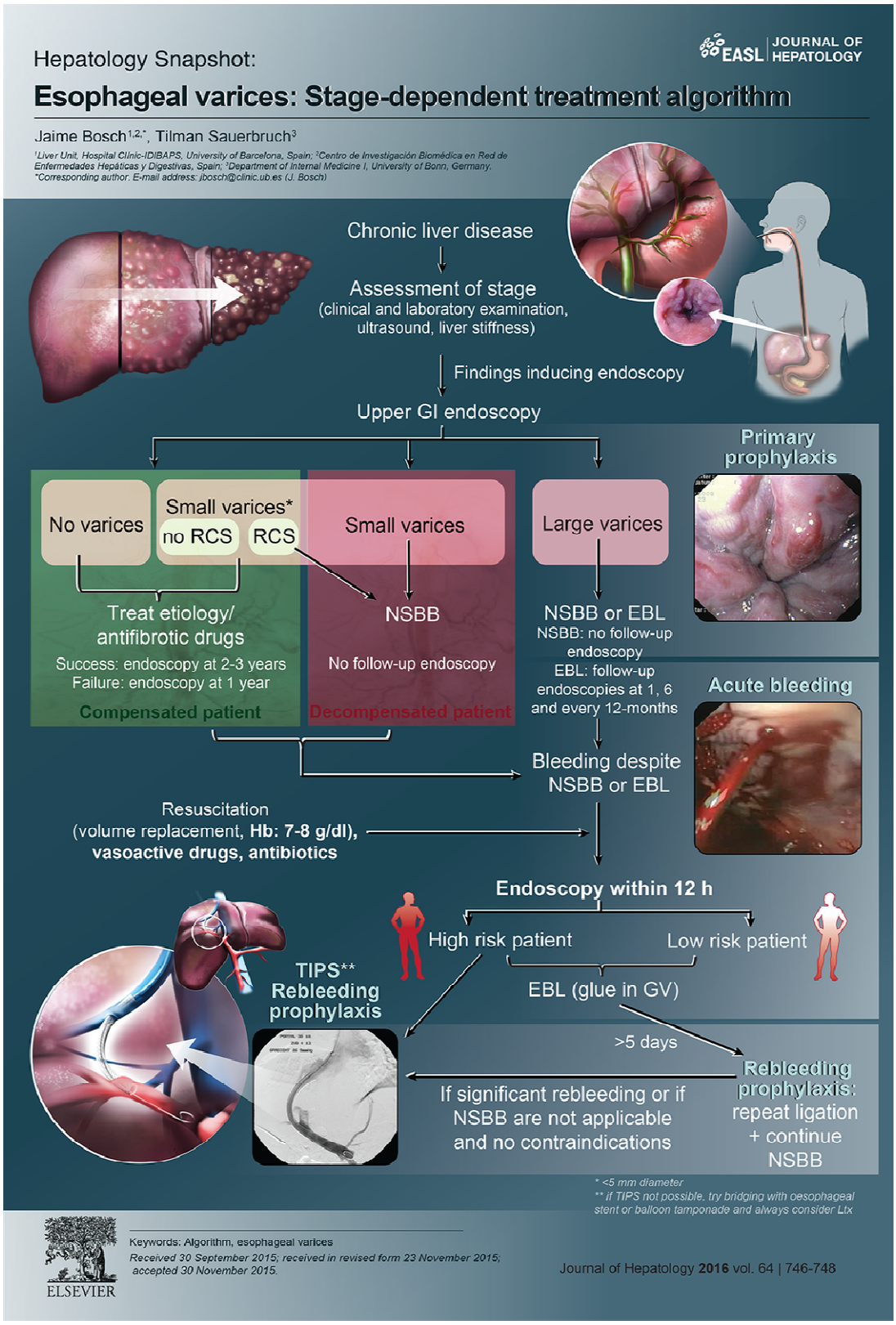


Figure 3: EASL Algorithm for management of Esophageal varices.

NON- NSBB MECHANISMS

Non selective beta blockers may also help in areas other than just reduction of portal pressure, like in ascites, hepatorenal syndrome, Hepatic encephalopathy and spontaneous bacterial peritonitis. In a promising research work by Abraldes et al it was reported that non selective beta blockers had a positive role in preventing ascites, Spontaneous bacterial peritonitis and hepatic encephalopathy [39].(Table 2)

Table : 2 Factors Independently Associated with the Analyzed End Points[39]

	RH	95% CI	*P* Value
Rebleeding			
Lack of hemodynamic response	2.804	1.107-7.104	.028
Albumin (g/L)	0.928	0.865-0.995	.030
Ascites			
Lack of hemodynamic response	3.483	1.265-9.587	.009
Platelet count ($\times 10^9$/L)	0.985	0.971-0.999	.016
Spontaneous bacterial peritonitis			
Lack of hemodynamic response	8.687	1.080-69.886	.016
Prothrombin rate (%)	0.950	0.904-0.998	.027
Hepatic encephalopathy			
Bilirubin (mg/dL)	2.617	1.069-6.408	.008
Survival			
Lack of hemodynamic response	12.387	1.555-98.690	.001
Age (y)	1.117	1.026-1.216	.008
Albumin (g/L)	0.903	0.824-0.990	.026

Analyzed with Cox proportional hazards model. The value of relative hazard indicates the relative risk or the strength of association of each variable adjusted by the other significant variables. Values above 1 indicate increased risk of reaching the end point. Values lower than 1 indicates protective effect. Abbreviation: RH, relative hazard.

Similarly in another study by Hernandez-Gea et al, showed that patients who had compensated cirrhosis and bigger varices, a reduction in the hepatic venous portal

gradient more than ten percent was enough to decrease the risk of developing ascites and other complications such as refractory ascites and HRS [40].

These studies and their findings suggest that beta blockers may benefit cirrhotic patients in non portal ways, reducing the risk of ascites, refractory ascites, spontaneous bacterial peritonitis hepatic encephalopathy and hepatorenal syndrome. In the recent times, much interest has been focused on infections in cirrhotics [41-43]. Infections in patients with liver disease pose a severe and frequent burden on the health care system as well as the patient's economy. In about, 40 % of patients admitted with cirrhosis in hospitals have infectious etiology which in turn leads to prolonged periods of hospitalization and also they carry an increased risk for death, around 15 %.[44,45]. Not only bacterial infections directly contribute to morbidity and mortality, it has also been found in a few studies, that they cause increased upper gastrointestinal bleeding [46,47], difficulty in managing variceal bleeders with failures [48] and increased early variceal re - bleeding rates.[49]. Also importantly the occurrence of bacterial infections serves as an important time point in the natural course of cirrhosis where the mortality is thiry percent at one month and doubles at one year. [50].

BACTERIAL TRANSLOCATION

In patients with cirrhosis, quite a significant number of infections is believed to because of bacterial translocation (BT), defined as the migration of microorganisms or microbial products from the intestinal lumen to the mesenteric lymph nodes or other extra-intestinal sites [51,52] (Fig 4).

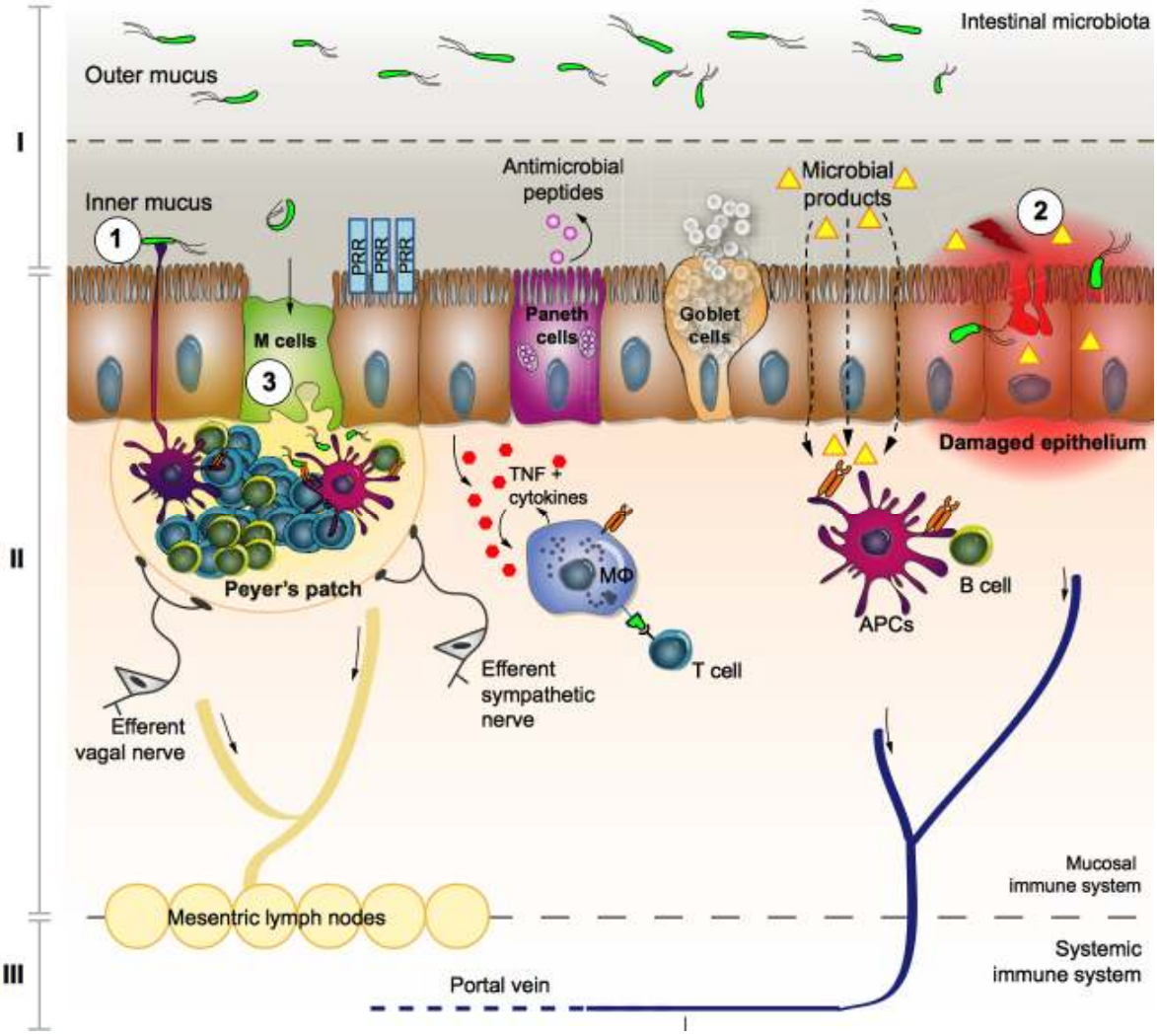


Figure 4: Compartments and key players involved in mediating pathological BT and the associated host response [53]

Three different routes of bacterial translocation can be separated:

(1) Direct sampling of luminal bacteria (l products) by dendritic cells via processes between epithelial cells, not affecting tight junction function

(2) injured/inflamed epithelium with dysfunctional epithelial barrier and

(3) M-cells overlying Peyer Patches as specialized cells providing access of microbial products to antigen-presenting cells.

As cirrhosis worsens, there is a parallel increase in the sympathetic activity as well. The sympathetic fibers converge on blood vessels, gut associated lymphatic tissue and the gut mucosa. There is increased availability of norepinephrine which slows the bowel motility, alters the mucosal barrier and blocks chemotaxis and phagocytosis. [54].

Adding to the above, the raised portal pressure increases intestinal membreane permeability by reducing the velocity of blood flow in the mucosal membrane.. This leads to phlebectasia and congestion of sub-mucous capillaries and veins [55]. So when the total splanchnic blood flow increases due to vasodilatation [56], an erratic distribution in the microcirculation occurs resulting in a decrease in the effective mucosal blood flow causing hyperemia, edema, ischemia, and potentially erosions [55].

ROLE OF NON SELECTIVE BETA BLOCKERS IN BACTERIAL TRANSLOCATION

Non selective beta blockers play a role in preventing bacterail transllocation. This occurs by its nature to reduce the portal pressure and reduce the intestinal permeability , thereby decreasing gut mucosal congestion and edema. A seen ealier, there is increased gut permeability that leads to endotoxemia. This is tackled by beta blockers.

In experimental animal models with portal hypertension, propranolol has been shown to increase bowel transit. Also it decreased the small intestinal bacterial overgrowth and its migration into the systemic circulation and thereby preventing the development of Spontaneous Bacterial Peritonitis [57].

But the same results are not directly available from human studies. Currently the only data that is available are *post-hoc* analyses that have been done on beta blockers in relation to development of spontaneous bacterial peritonitis. [59, 60, 61]. So the evidence is all coming as derived interpretation, that patients taking non selective beta blockers may have a diminished incidence of spontaeous bacterial peritonitis. Cholongitas and his colleagues also confirmed the same concepts in a recent meta-analysis . [58].

Intestinal permeability can be assessed by ucorse - lactulose mannitol test. Bacterial translocation can be assessed by measuring the levels of lipopolysaccharide-binding protein, interleukin-6 and malondialdehyde. Reiberger et al in a recent study [62], had researched on the effects of propranolol on

intestinal permeability and bacterial translocation. In this study, they had arrived at the conclusion that NSBB are able to ameliorate intestinal permeability and Bacterial Translocation in cirrhotic patients [62]. Of particular importance, this preventive effect seemed to be independent of their hemodynamic effect on portal pressure, reinforcing the hypothesis that non selective beta blockers also serve by non-hemodynamic mechanisms. Even further, this concept is augmented by the fact that patients, even when patients do not have a good hemodynamic response to beta blockers , still they had a reduced risk of bleeding which seems to have no clear explanation.[63]. In the study by Turnes et al, it was shown that when the hepatic venous pressure gradient fell by eleven percent , which is suboptimal hemodynamic response , still the patients had a reduced incidence of spontaneous bacterial peritonitis. [59]. So it is very much possible that there is much more to non selective beta blockers benefits in cirrhotics, than just mere reduction in the portal pressure.

NON SELECTIVE BETA BLOCKERS IN REFRACTORY ASCITES

The effects of non elective beta blockers on refractory ascites are still under debate. While NSBB reduce cardiac output and splanchnic blood flow, it may be harmful in decompensated cirrhotics especially with refractory ascites. There exists already a cardiac impairment in advanced cirrhosis, the cirrhotic cardiomyopathy which consists of stress induced systolic incompetence, diastolic dysfunction, and electrophysiological abnormalities [69,70,71]. The underlying mechanism in cirrhotic cardiomyopathy involves abnormal signaling in the beta adrenergic pathway ,increased sodium , plasma expansion and the presence of

substrates that have a negative ionotropic effect. All these lead to cardiomyocyte hypertrophy which may possibly have an effect on the channel defects [72,73]. Most of the time, the cardiomyopathy part is well tolerated and is not manifested clinically. But when there is a situation where the peripheral arterial vasodilatation becomes worse , as in the placement of a TIPS or a large volume paracentesis or spontaneous bacterial peritonitis where the endotoxins can cause vasodilatation , the hearts systolic incompetence becomes clinically evident[74,75,76]. Theoretically if one uses a non selective beta blocker in this situation, it would add more damage. Lebrec et al, who was the first to demonstrate usefulness of beta blockers for portal hypertension also researched on the hemodynamic effects and the impact on survival of non selective beta blockers use in patients with refractory ascites [3, 4]. The study had 151 patients enrolled , half of whom had large esophageal varices that required treatment with non selective beta blockers , whereas only 4 patients did take NSBB without any varices. The reasons for the staring of beta blockers in both of the situations were

not clearly mentioned.

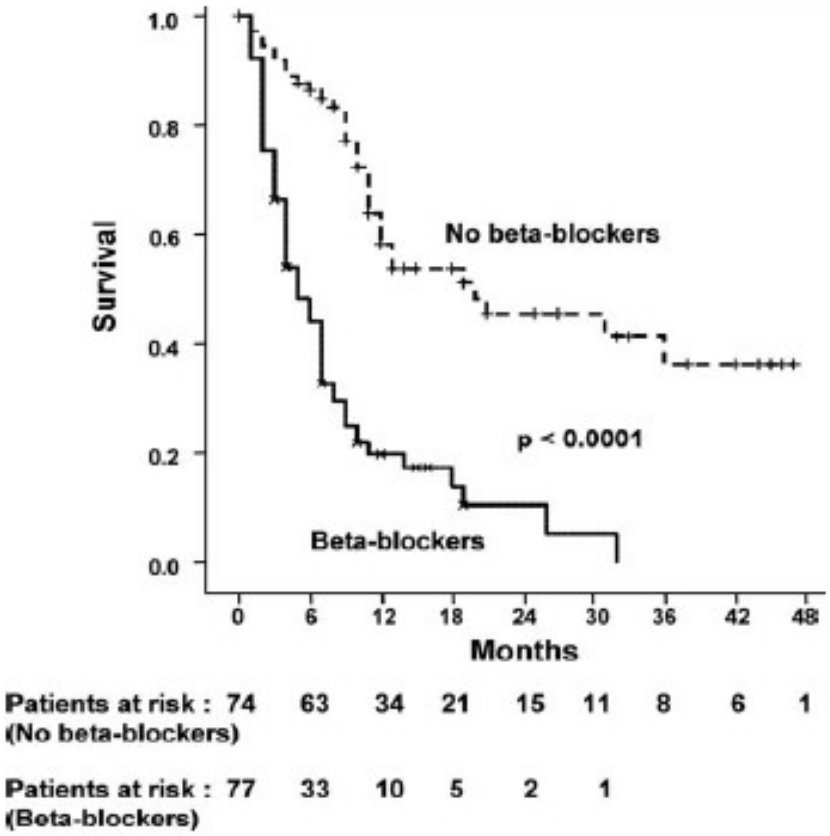


Figure 5 Serste et al, Hepatology.Survival analysis.

It was reported to be a median survival of five months in patients taking beta blockers while those not taking beta blockers had a median survival of 20 months.(Fig 5)The authors opined that the use of NSBB in decompensated cirrhotic patients with refractory ascites might be dangerous. The results of these studies though initially created alarm, was later criticized because of its observational design and not a randomized controlled design. Also the gold standard of measuring portal hypertension, HVPG measurement was done only in a small number of the patients.. The difference in the hepatic venous pressure

gradient was expected, because of the prevalence of varices. Another criticism arose regarding the cause of deaths in which 25 were unknown. These were in contrast to previous findings in which NSBB had a protective role against infections. Also the mortality rates were higher when compared to previous studies [77,78].

The same group, to evaluate their hypothesis further, did a cross-over study to look at the impact of non selective beta blockers on the development of paracentesis induced circulatory dysfunction (PICD) [79]. PICD is a syndrome of circuatory disturbance typically occurring after large-volume paracentesis which is characterized by systemic vasodilatation and decrease in effective arterial blood flow. It is associated with reduced survival. They took 10 cirrhotic patients with refractory ascites taking non selective beta blockers. All underwent large volume paracentesis and beta blocker therapy was terminated after varices were eradicated by endoscopic variceal ligation. Clinical follow up and repeated paracentesis were done.

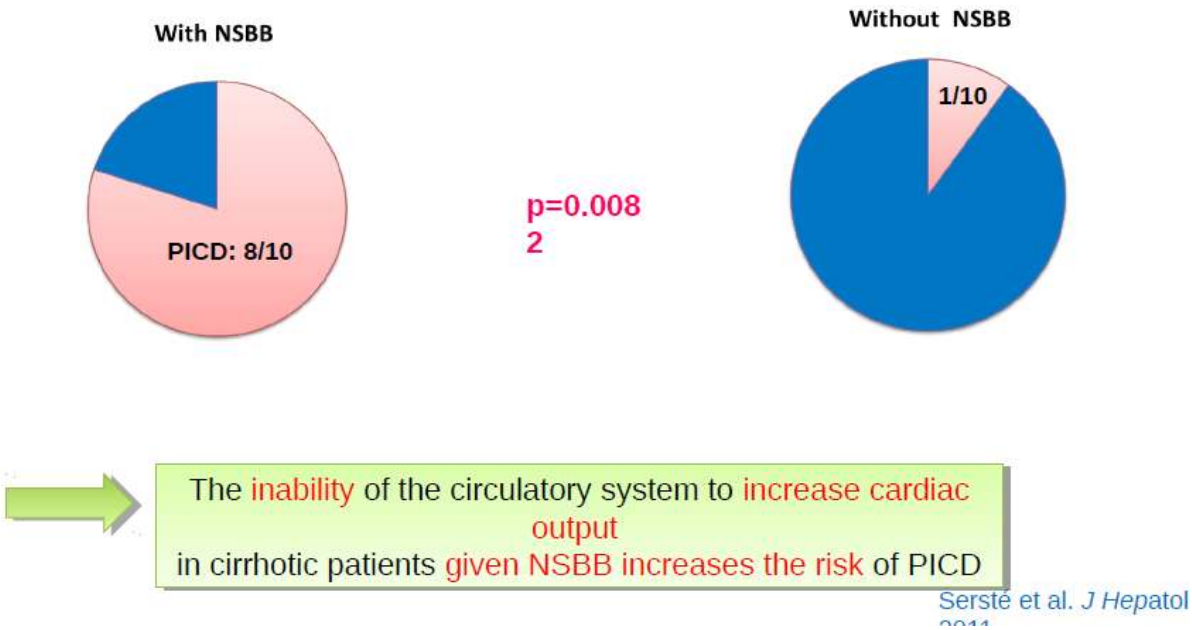
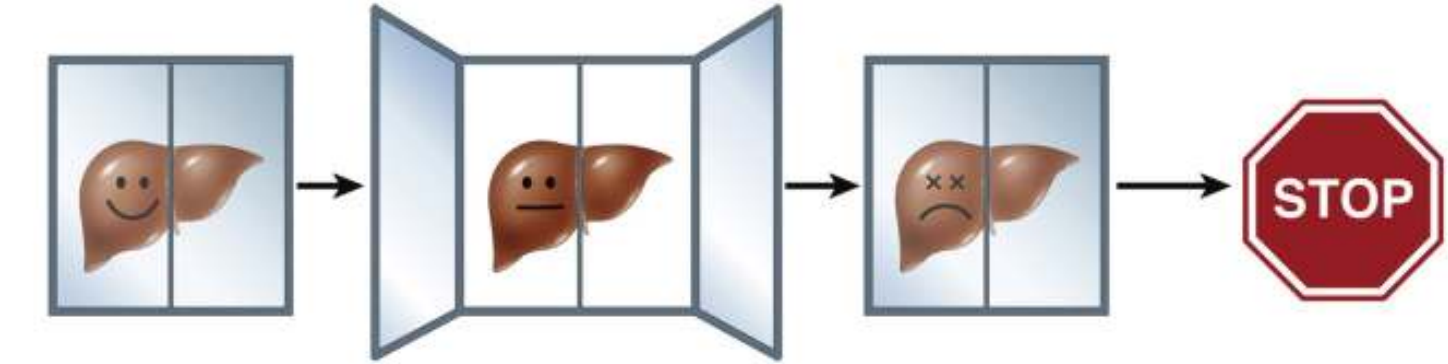


Figure 6: Serste et al , Hepatology. Incidence of Paracentesis induced circulatory dysfunction.

Incidence of PICD remarkably reduced from eighty percent to ten percent when the non selective beta blockers were stopped. This suggested that beta blockers negatively affect the hemodynamic status which is already compromised in patients with advanced cirrhosis(fig 6). However, these results cannot be extrapolated to the clinics, considering the small sample size. Much more studies are needed, before one can withdraw beta blocker therapy in a patient with End stage liver disease (ESLD).

BETA BLOCKER WINDOW HYPOTHESIS

In the work by Lebrec's group , arose the concept of the β-blockers 'therapeutic window' hypothesis in cirrhosis [80]. This hypothesized that, non selective beta blockers have no effects in early cirrhosis because the so called clinically significant portal hypertension (HVPG≥10 mm Hg) has not yet been reached and there are no medium or large varices and sympathetic nervous system (SNS) activity is also remaining normal [81]. As the disease worsens, the portal pressure worsens, splanchnic hyperemaia ensues , sympathetic activity increases and bacterial translocation increases. At this point, the therapeutic window opens and current guidelines recommend prophylaxis with NSBBs. Further in the disease course, the peripheral arterial dilatation becomes prominet. Blood pressure (BP) and organ perfusion integrity become critically dependent on cardiac output. So at this stage, knocking out the cardiac output by beta blockers would lessen the survival and is unfavourable [82,83,84]. Even more, in refractory ascites there is a decreased sensitivity to the β-adrenergic blockade in favour of the α-adrenergic blockade secondary to raised levels of splanchnic proinflammatory cytokines, with a resulatnt reduction in NSBBs' beneficial effects [85].(Fig 7) In this stage, using non selective beta blockers could be harmful. The therapeutic window closes theoretically. But still there have been many studies refusing this theory and the exact role of NSBBs needs further clarification.



Early cirrhosis	Window opens	Window closes	Window does not re-open
• Beta-blockers are **not indicated** in early cirrhosis, may increase adverse events • Beta-blockers **may be indicated** for cardiovascular indications	• Beta-blockers are **indicated** for primary prophylaxis of variceal bleeding • Beta-blockers are **indicated** for secondary prophylaxis of variceal bleeding	• Beta-blockers are **contraindicated** under the following situations: ◦ Refractory ascites ◦ Systolic blood pressure < 100mm Hg ◦ Mean arterial pressure < 82mm Hg ◦ Acute kidney injury ◦ Hepatorenal syndrome ◦ **Spontaneous bacterial peritonitis** ◦ Sepsis ◦ Poor medical follow-up ◦ Patient noncompliance	

Figure 7: The window hypothesis

HEPATORENAL SYNDROME AND AKI

Hepatorenal syndrome (HRS) is a distinct cause of renal impairment of functional origin that occurs in patients with liver cirrhosis (Fig 8). But patients with cirrhosis can also develop Acute Kidney Injury (AKI) besides Hepatorenal Syndrome due to other causes, such as prerenal azotemia, intrinsic acute kidney injury, sepsis, nephrotoxic drugs, and parenchymal nephropathy [86,87]. AKI must be differentiated from HRS because the treatments differ. Here come in the role of biomarkers that help categorize the type of renal failure and predict or stage renal dysfunction. Lot of studies have reported the potential of NGAL as an early marker in the differential diagnosis of AKI in cirrhosis [88]. Another molecule, CysC a non-glycosylated protein is thought to be a more reliable marker of glomerular filtration rate (GFR) as it is less influenced by age, sex, muscle mass, or serum bilirubin levels than serum creatinine. However, results in patients with cirrhosis are limited and nonconclusive.

In a study by Ruiz-del-Arbol et al (92), he reported that patients who had spontaneous bacterial peritonitis , developed renal impairment in association with decreased cardiac output and mean arterial pressure which makes plausible why NSBB therapy would be dangerous for survival of patients with fairly advanced cirrhosis. Similar studies have induced authors to reconsider peripheral vasodilation hypothesis, adding to the widely accepted cascade of a final stage characterized by a hyperdynamic circulation that comes down as a consequence of a relative failure of cardiac output(93).So, the negative inotropic and hypotensive effects of NSBBs could be deleterious for patients with advanced

cirrhosis and refractory ascites and/or HRS. But surprisingly, many other research have continued to prescribe NSBBs to patients with advanced cirrhosis proposing that the methodological quality of the available research materials are not enough to making the results reliable (94).

Therefore, the use of NSBBs in patients with advanced cirrhosis has become an issue of debate between those who are concerned upon the safety of NSBBs given to patients with severe cirrhosis and those who critics the quality of the methods used to generate the evidence of negative effects of NSBBs in cirrhosis.

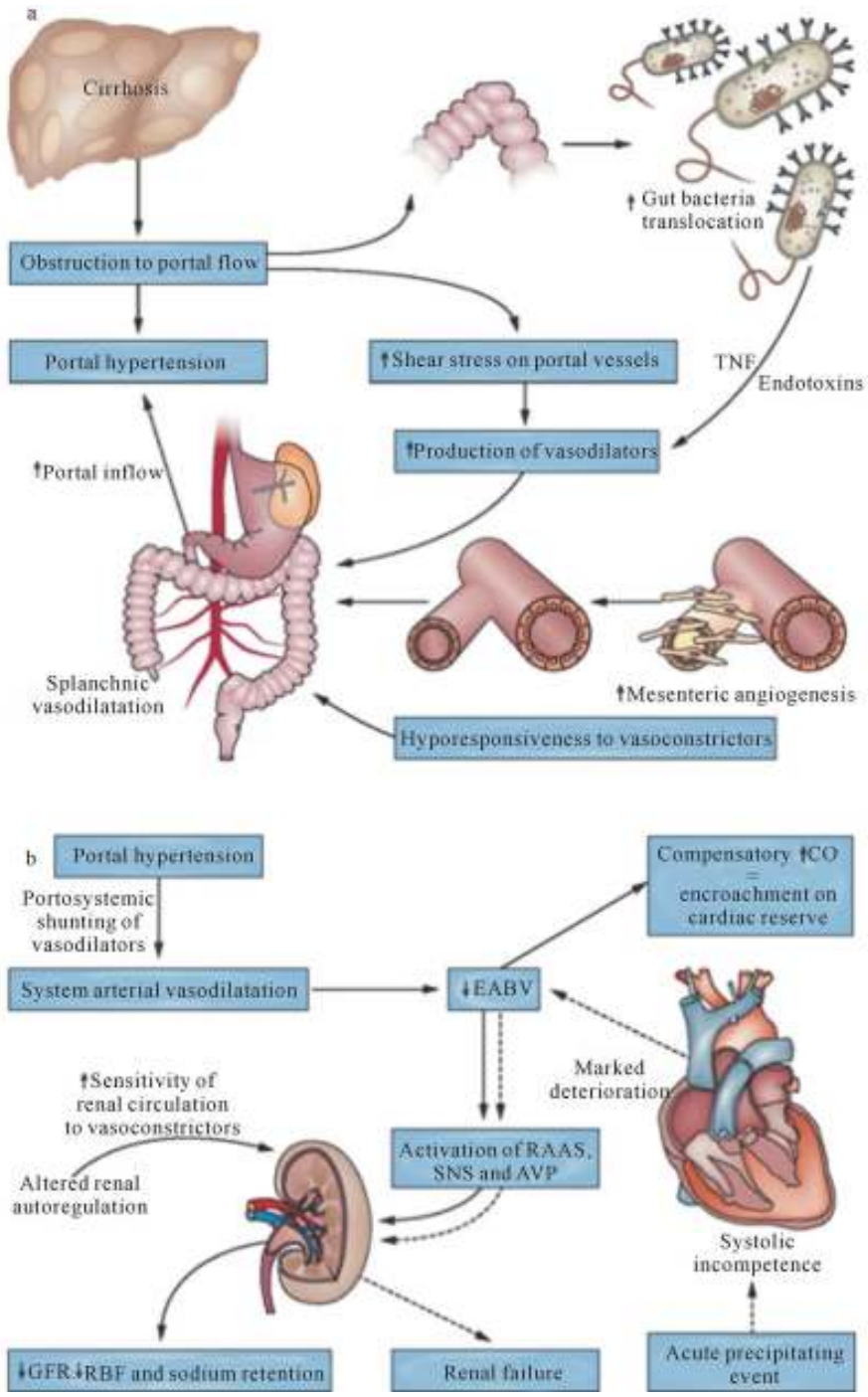


Figure 8: Pathophysiology of Hepatorenal syndrome.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) encompasses all the neuropsychiatric abnormalities that develop in the setting of portal hypertension. Overt HE develops in 30–45 % of patients with cirrhosis [32]. Subclinical HE is more subtle and characterized by psychomotor slowing, visuoconstructive disabilities, and attention deficits. It is present in up to 80 % of cirrhotics [90]. Hepatic Encephalopathy is precipitated by neurotoxins normally cleared by the liver, but that are shunted around the liver in the presence of portal hypertension-induced portosystemic collaterals, allowing them to influence the central nervous system. (fig 10). Patients hospitalized with HE experience mortality rates of 42 % at 1 year and 23 % at 3 years [91]. Commonly used test to detect at bed side which is easily available is the psychometric tests (Fig 9).

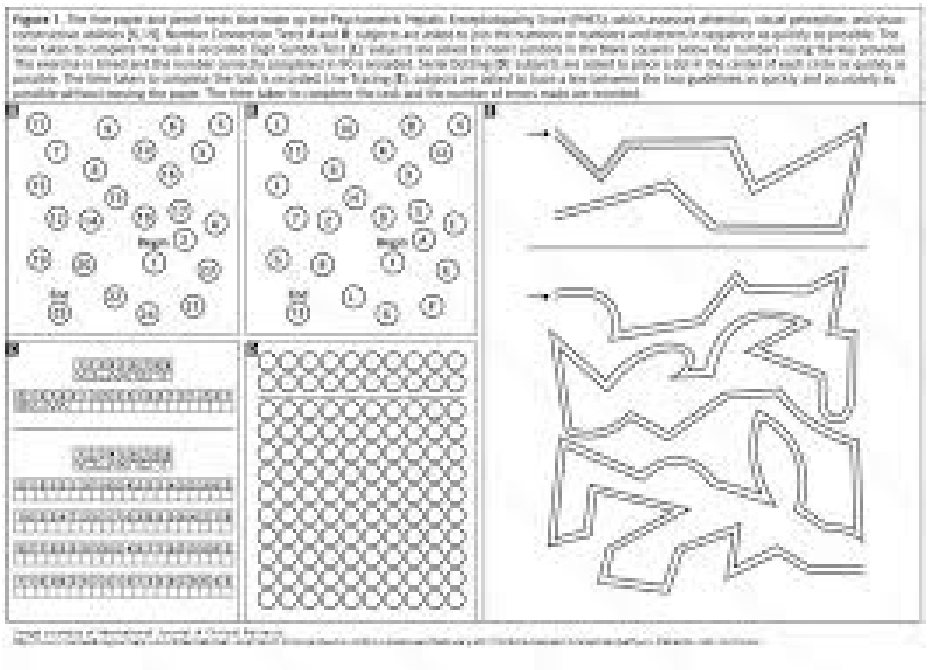


Figure 9: Psychometric Encephalopathy Score tests.

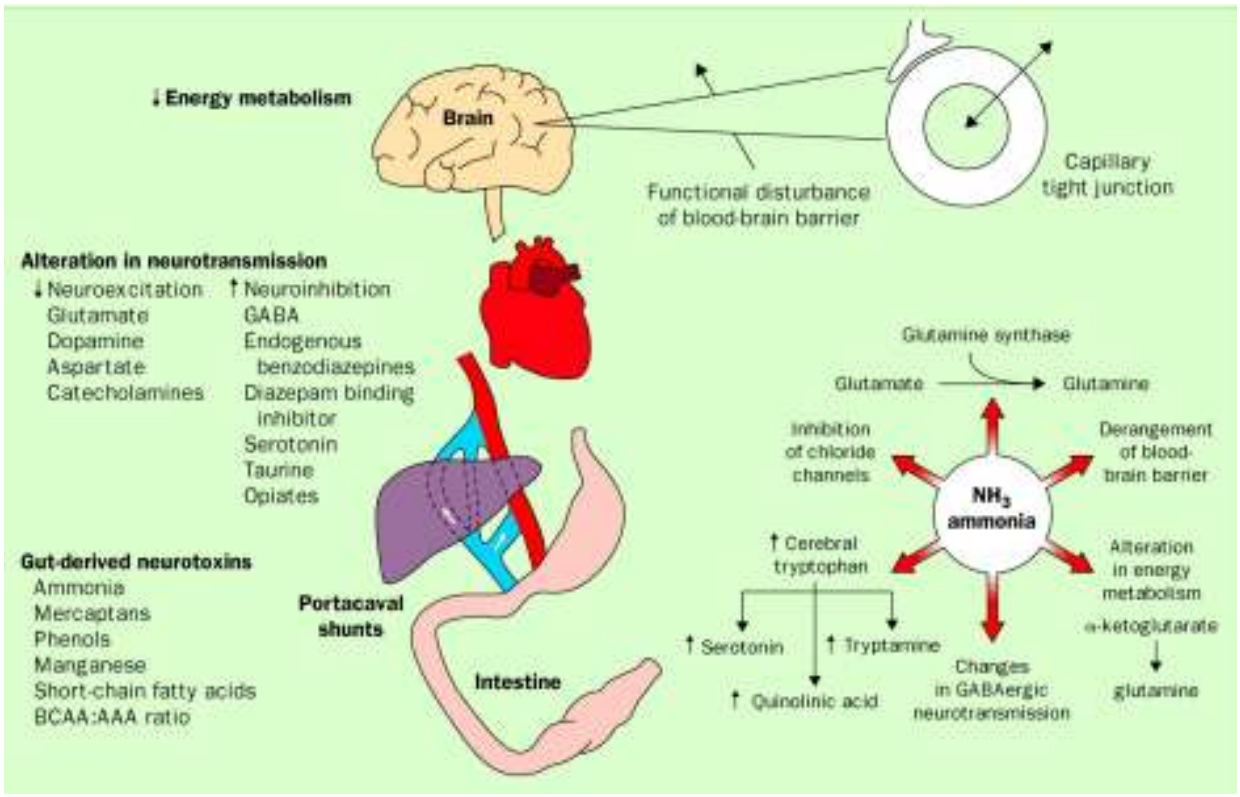


Figure 10: THE LANCET - Pathophysiology of Hepatic Encephalopathy

AIMS AND METHODOLOGY

AIM OF THE STUDY

Aimed to analyze the impact of beta blockers on the following complications in cirrhosis:

1. Spontaneous bacterial peritonitis (SBP)

2. Refractory ascites

3. Hepatorenal syndrome (HRS) and

4. Hepatic encephalopathy (HE)

in patients who did or did not take non-selective beta blockers and thereby to test the null hypothesis that beta blockers cause worsening of the above mentioned complications.

MATERIALS AND METHODS

Study Design : Single centre, case control retrospective study.

Study centre : Department Of Digestive Health and Diseases, Kilpauk Medical College and Hospital, Kilpauk Medical College, Chennai.

Period of Study : 2 years (January 2015 to January 2017)

Study population : In Patients and Outpatients having cirrhosis and portal hypertension who were registered with the Department of Digestive Health and Disease between the period January 2009 to January 2016.

Inclusion criteria : Patients having cirrhosis with portal hypertension.

Exclusion criteria : Patients who had significant cardiovascular disease, extrahepatic malignancy, intrinsic renal disease and those not willing to provide consent were excluded from this study.

Financial Assistance : Nil

METHODOLOGY

Patients were identified from a prospectively collected data base. The following parameters were recorded at the time of enrollment to study: age, sex, duration of disease, number of hospital admissions for cirrhosis related illnesses, history of diabetes, history of upper gastrointestinal bleeding, presence of cirrhotic cardiomyopathy, portal vein thrombosis. Biochemical parameters such as complete blood count, renal function test, and liver function test were done. The MELD[5] and CTP[6,7] score were calculated based on the bilirubin, creatinine, PT/INR, albumin, presence of ascites and Hepatic Encephalopathy.

Esophagogastroduodenoscopy was done in all patients and esophageal varices[9,10], gastric varices[8] and portal hypertensive gastropathy[11] were identified and graded accordingly. The occurrence of spontaneous bacterial peritonitis, refractory ascites, hepatorenal syndrome and hepatic encephalopathy were also noted.

The diagnosis of spontaneous bacterial peritonitis and encephalopathy were based on clinical, biochemical and microbiologic data as interpreted by the treating physician.

Refractory ascites and hepatorenal syndrome were diagnosed by the definitions proposed by the International Ascites Club.

The International Ascites Club criteria for Hepatorenal Syndrome is as follows :

1. Presence of cirrhosis and ascites

2. Serum creatinine >1.5 mg/dL (or 133 micromoles/L)

3. No improvement of serum creatinine (decrease equal to or less than 1.5 mg/dL) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (recommended dose: 1 g/kg b.w. per day up to a maximum of 100 grams of albumin/day)

4. Absence of shock

5. No current or recent treatment with nephrotoxic drugs

6. Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 RBCs/high power field, and/or abnormal renal ultrasound scanning.

Refractory ascites was defined as that ascites which recurred early , cannot be mobilized and not prevented by medical therapy. It is of two types :

1. Diuretic intractable , which is the condition in which diuretics dosage cannot be increased due to diuretics induced complications.
2. Diuretic resistant , which is the state where maximum dose of diuretics has been used , but still fails to mobilize ascetic fluid.s

Echocardiogram and electrocardiogram were also done in all patients to look for cirrhotic cardiomyopathy. Portal Venous Doppler (PVD) was also done to look for portal venous thrombosis.

PROFORMA

Name : Age: Sex: DDHD no:

Duration of illness: Etiology of cirrhosis: No of hospital admissions:

Comorbid illness:

Medications:

Beta blockers : yes/ no

MELD score: CTP Score: DF:

Previous history of GI bleed and therapy :

Presence of HRS:

Presence of Hepatic Encephalopathy:

Presence of Refractory Ascites:

Presence of Spontaneous bacterial peritonitis:

INVESTIGATIONS

Bili total		Hb%		HBsAg		USG abdomen
Bili direct		TC		Anti-HCV		
SGOT		DC		HIV		
SGPT		Platelets		PT/INR		
SAP		Urine alb		MHE		Portal Doppler
Tot prot		RBS		ECG		
S.alb		Bl.urea		Echo		
S.glob		S.creat				

Esophago gastroduodenoscopy:

Presence of varices: Grading :

Ascitic fluid analysis:

TC DC Protein Albumin SAAG Cytology

Culture and sensitivity

STATISTICS

Statistical analysis was done using SPSS software version 2.0. All quantitative data were expressed in Mean ± SE. Chi square analysis was done to compare the frequency of complications in the NSBB and non - NSBB groups. $P< 0.05$ was considered significant.

RESULTS

Demographic data:

A total of 82 patients were included in this study. The mean age of the entire cohort was 47.91 years. Predominantly our cohort had male patients (n= 65, 79.3%) (Fig 11). The overall mean duration of disease was 1.5 years.

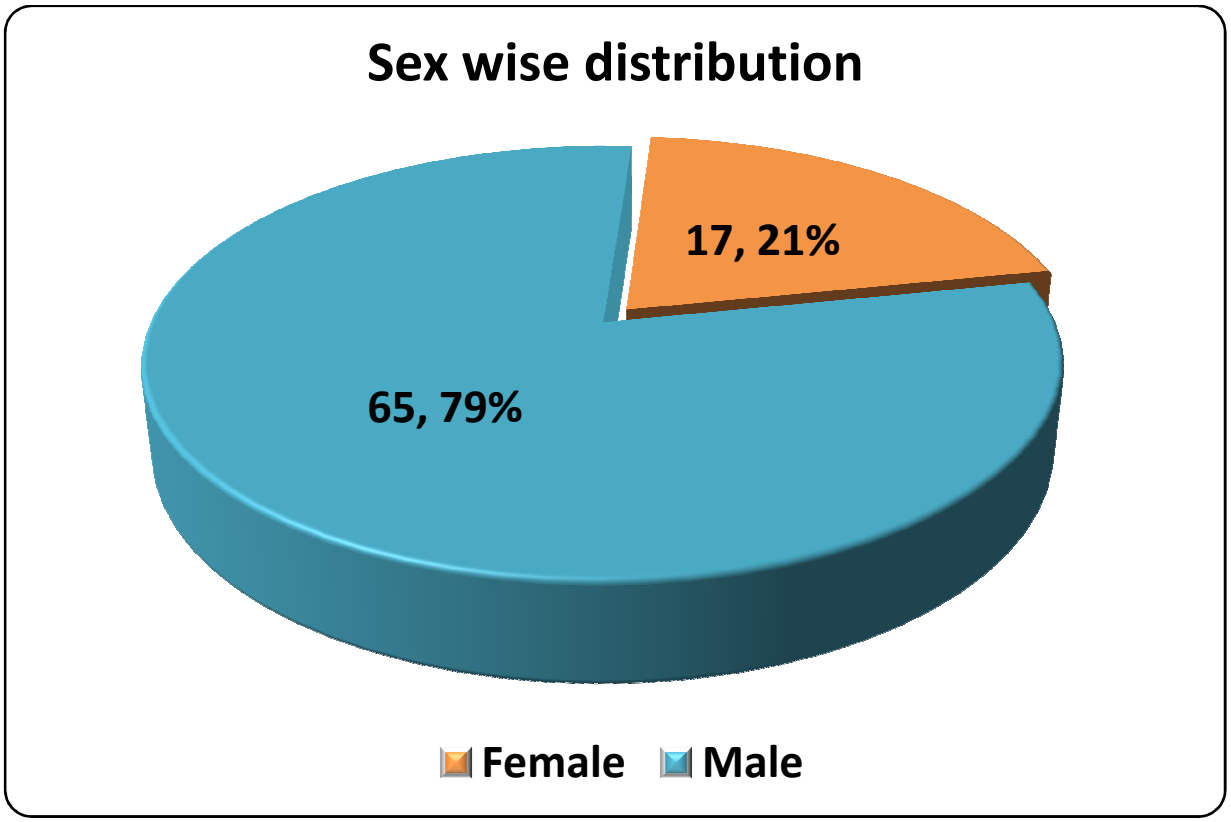


Figure 11: Sex wise distribution

The common etiology for liver cirrhosis was ethanol (n = 61, 74.39%), followed by Chronic viral Hepatitis B (n = 9, 10.97%) cryptogenic, non alcoholic steatohepatitis and Hepatitis C. Four patients had both Hepatitis B and significant alcohol consumption .

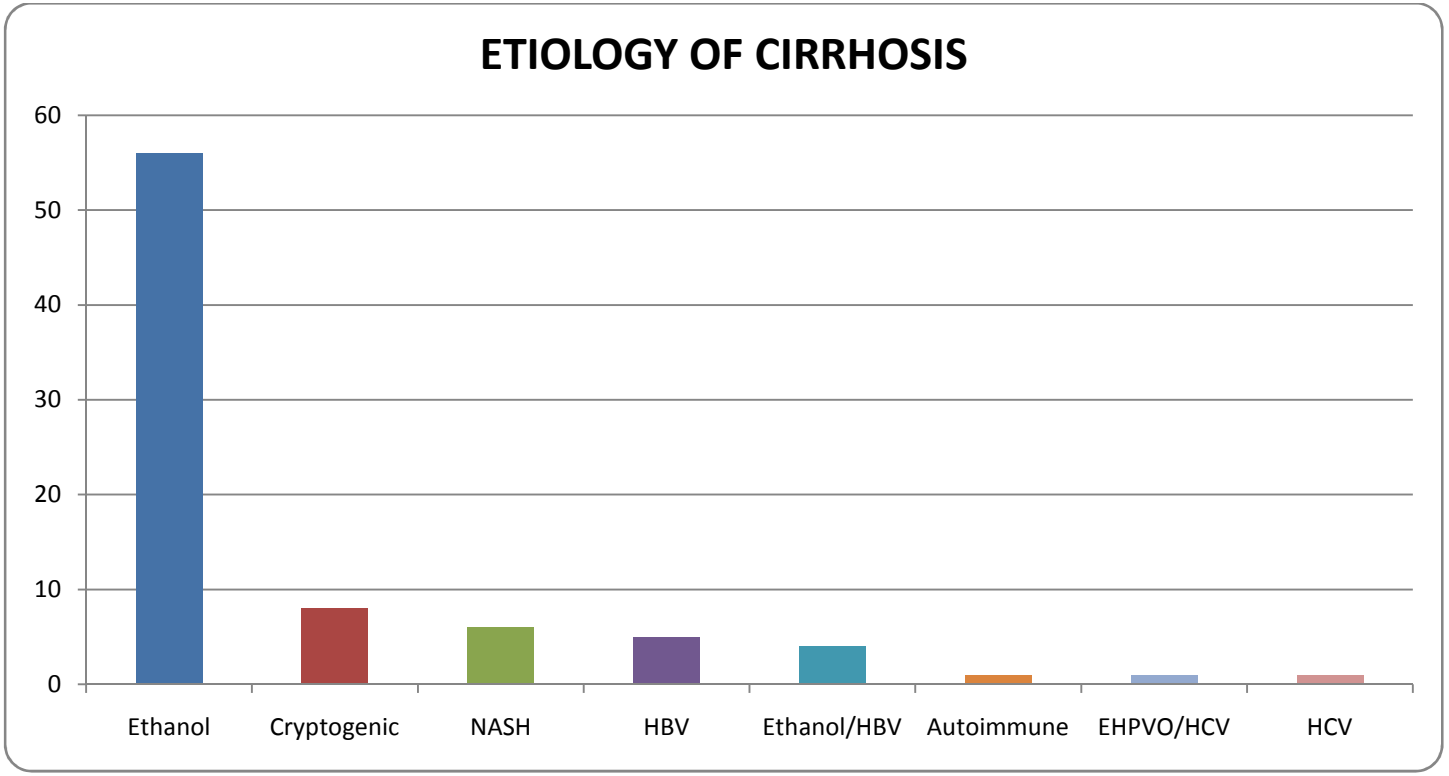


Figure 12: Etiology of cirrhosis

Of the 82 patients, 44 patients (53.6 %) were on non selective beta blockers and 38 patients (46.3%) were not on beta blockers

HOSPITALIZATION:

The numbers of hospitalizations were higher in patients taking beta blockers, when compared to those not taking it (Fig 14). But whether beta blockers directly/indirectly contributed cirrhosis related admissions cannot be concluded from this observation, because of several confounding factors like the severity of disease, high MELD / CTP , comorbidities, ongoing alcohol use and non compliance with drugs.

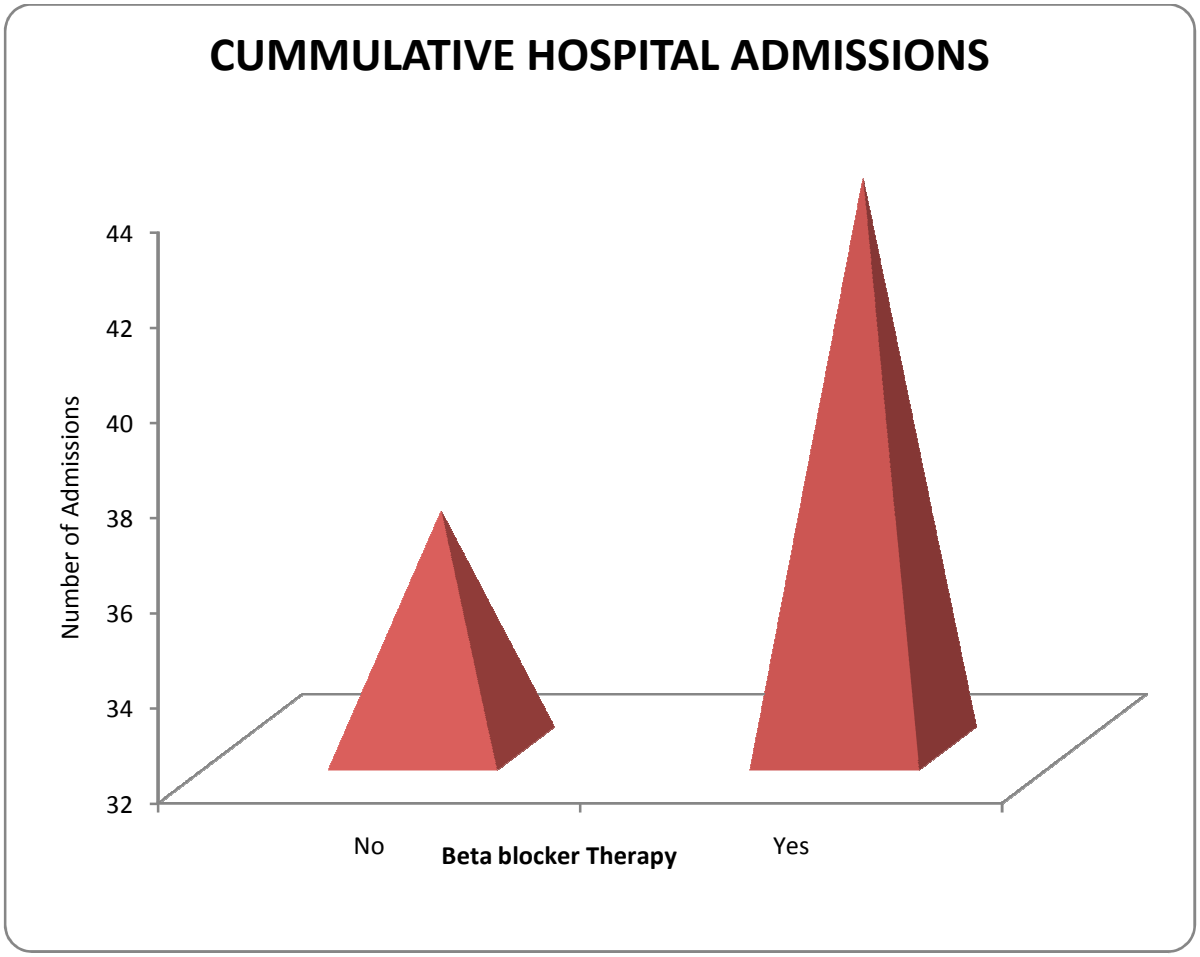


Figure 14: Cummulative Hospital Admissions

FREQUENCY OF UPPER GASTROINTESTINAL BLEED

41.66% of patients (n= 35) had a history of upper gastrointestinal bleeding in the past in the form of hemetemesis / melena or both. Predominantly the bleeders were from the NSBB group (n= 24, 68.6 %) and the non NSBB patients bled in few numbers (n= 11,31.4%) as one would expect, so the p value was significant (Fig15/Table 3).

Table 3: Number of bleeders in both groups

UGI BLEED	BETA BLOCKER		TOTAL	P-VALUE
	YES	NO		
YES	24(54.5%)	11(29.7%)	35(43.2%)	
NO	20(45.5%)	26(70.3%)	46(56.8%)	
TOTAL	44	37	81	0.025

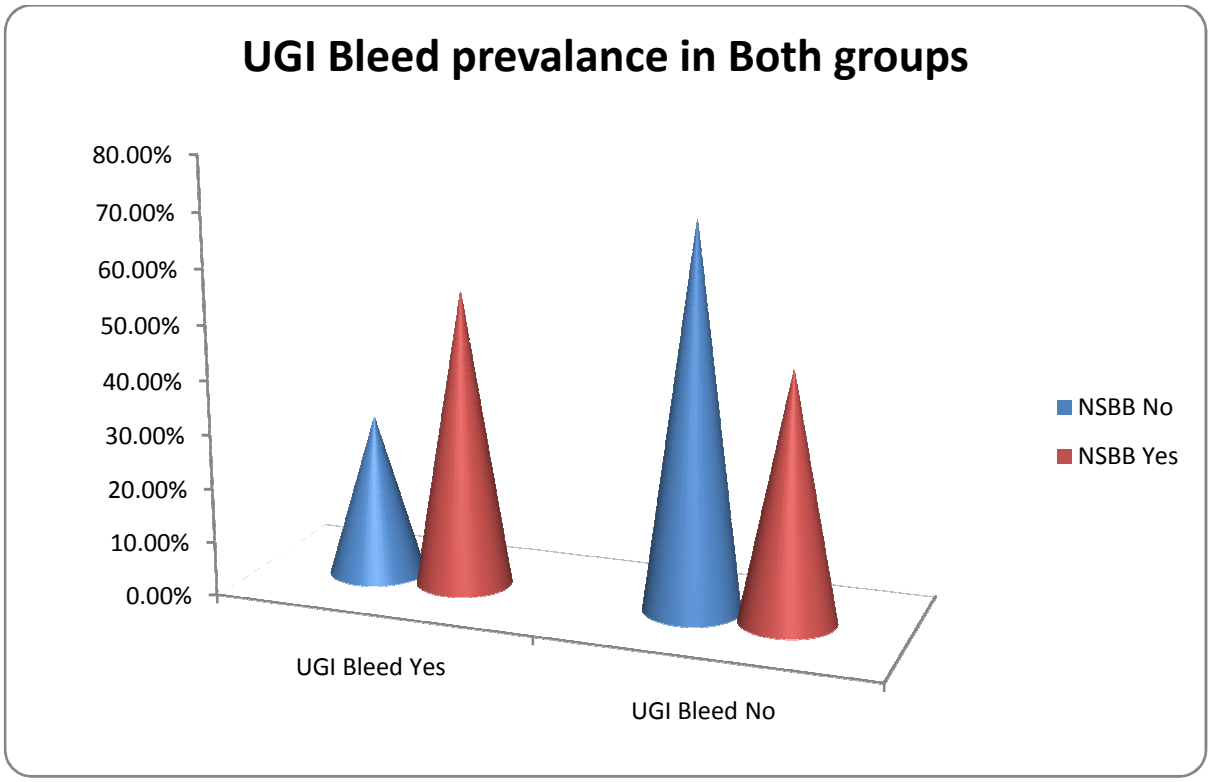


Figure 15: UGI bleeding in both groups

FREQUENCY OF DIABETES AMONG NSBB AND non NSBB PATIENTS

17 patients had diabetes (20.7%) in this study group. 11 patients (64.7 %) in the NSBB group and 6 patients (35.3%) in the non NSBB group had diabetes. Because diabetes can predispose to infections, this parameter was also included in the study. But the p value was 0.341 , when compared against both groups, suggesting that diabetes is not contributing to the complications of cirrhosis (Fig 16/Table 4).

Table 4: Number of Diabetes in both groups

DIABETES	BETA BLOCKER YES	NO	TOTAL	P-VALUE
YES	11(26.2%)	6(17.1%)	17(22.1%)	
NO	31(73.8%)	29(82.9%)	60(77.9%)	
TOTAL	42	35	77	0.341

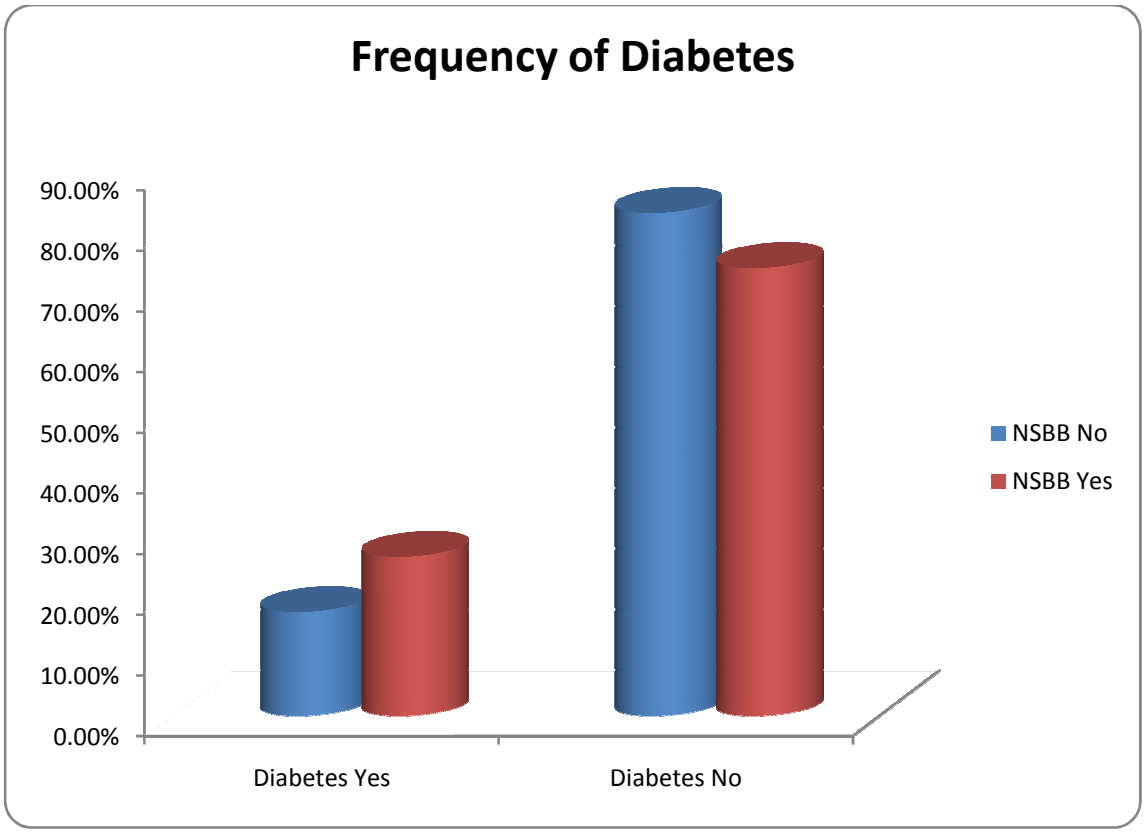


Figure 16: Diabetes in complications

FREQUENCY OF CIRRHOTIC CARDIOMYOPATHY AMONG NSBB AND non NSBB PATIENTS

Ten patients (12.2%) had cirrhotic cardiomyopathy. Those on beta blockers, 60 % (n=6) developed cirrhotic cardiomyopathy and 40 % (n= 4) of patients not taking non selective beta blockers developed cardiomyopathy. There are studies that have observed decreased QT intervals in cirrhotic cardiomyopathy while on beta blocker therapy (95.) In this study, such protective effect on the cardiac myocyte by beta blockers was not observed. (p=0.293) (Fig 17/Table 5).

Table 5: Cirrhotic Cardiomyopathy in both groups

CIRRHOTIC	BETA BLOCKER			
CARDIOMYOPATHY	YES	NO	TOTAL	P-VALUE
YES	6(30%)	4(16.7%)	10(22.7%)	
NO	14(70%)	20(83.3%)	34(77.3%)	
TOTAL	20	24	44	0.293

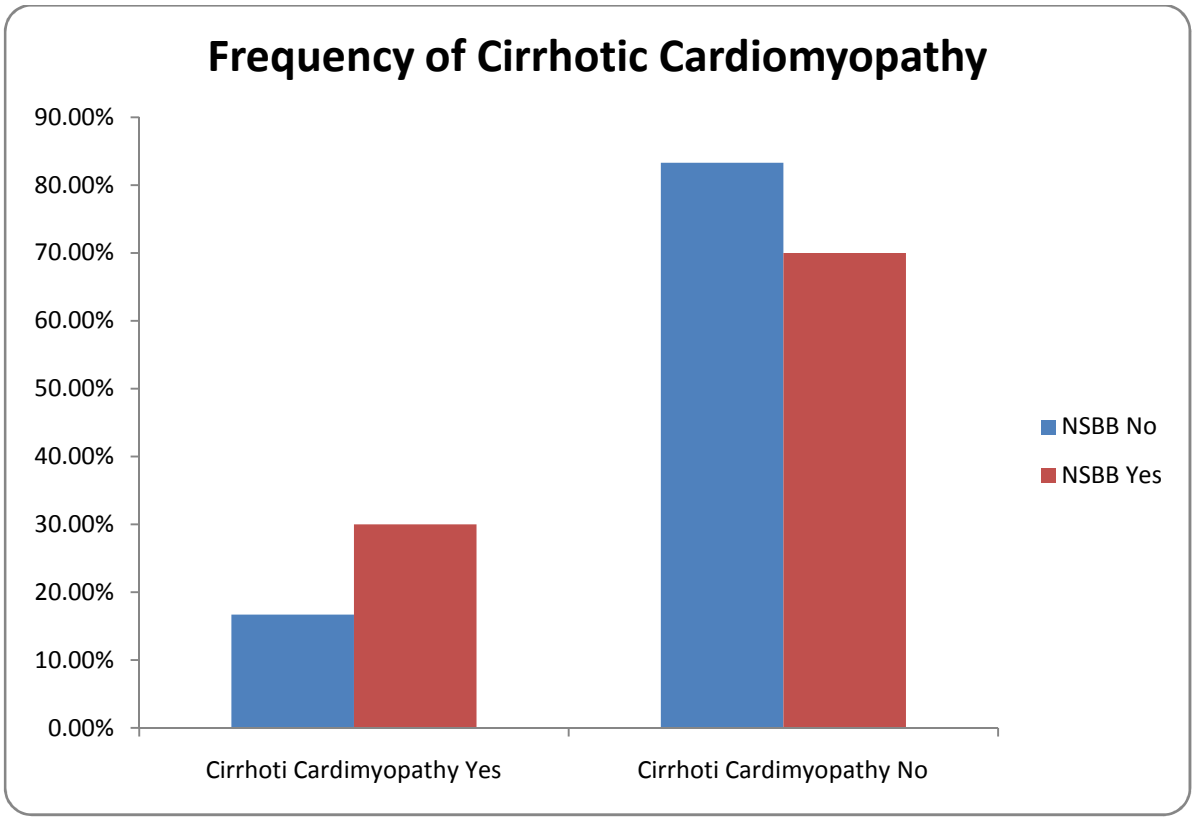


Figure 17: Frequency of cirrhotic cardiomyopathy

FREQUENCY OF PORTAL VEIN THROMBOSIS AMONG NSBB AND non NSBB PATIENTS

Only two patients (2.4%) in this study group had portal vein thrombosis(PVT). And both the patients were not on beta blockers. As mentioned earlier, few papers have suggested that beta blockers can also decrease the incidence of portal vein thrombosis. In our study, such a difference was not evident (p=0.167) (Fig 18/Table 6).

Table 6: Portal vein thrombosis in both groups

	BETA BLOCKER			
PVT	YES	NO	TOTAL	P-VALUE
YES	-	2(8.7%)	2(4.5%)	
NO	21(100%)	21(91.3%)	42(95.5%)	
TOTAL	21	23	44	0.167

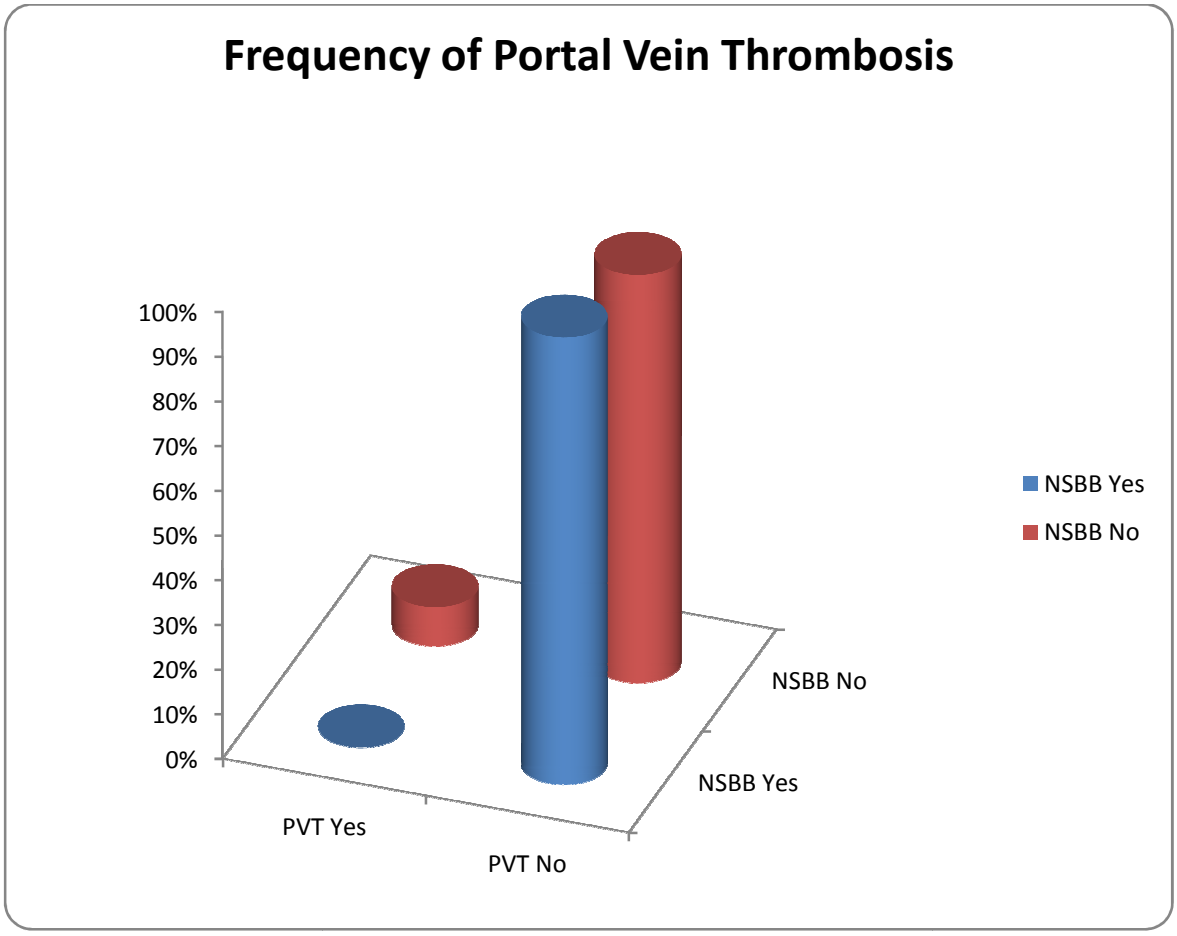


Figure 18:Frequency of portal vein thrombosis

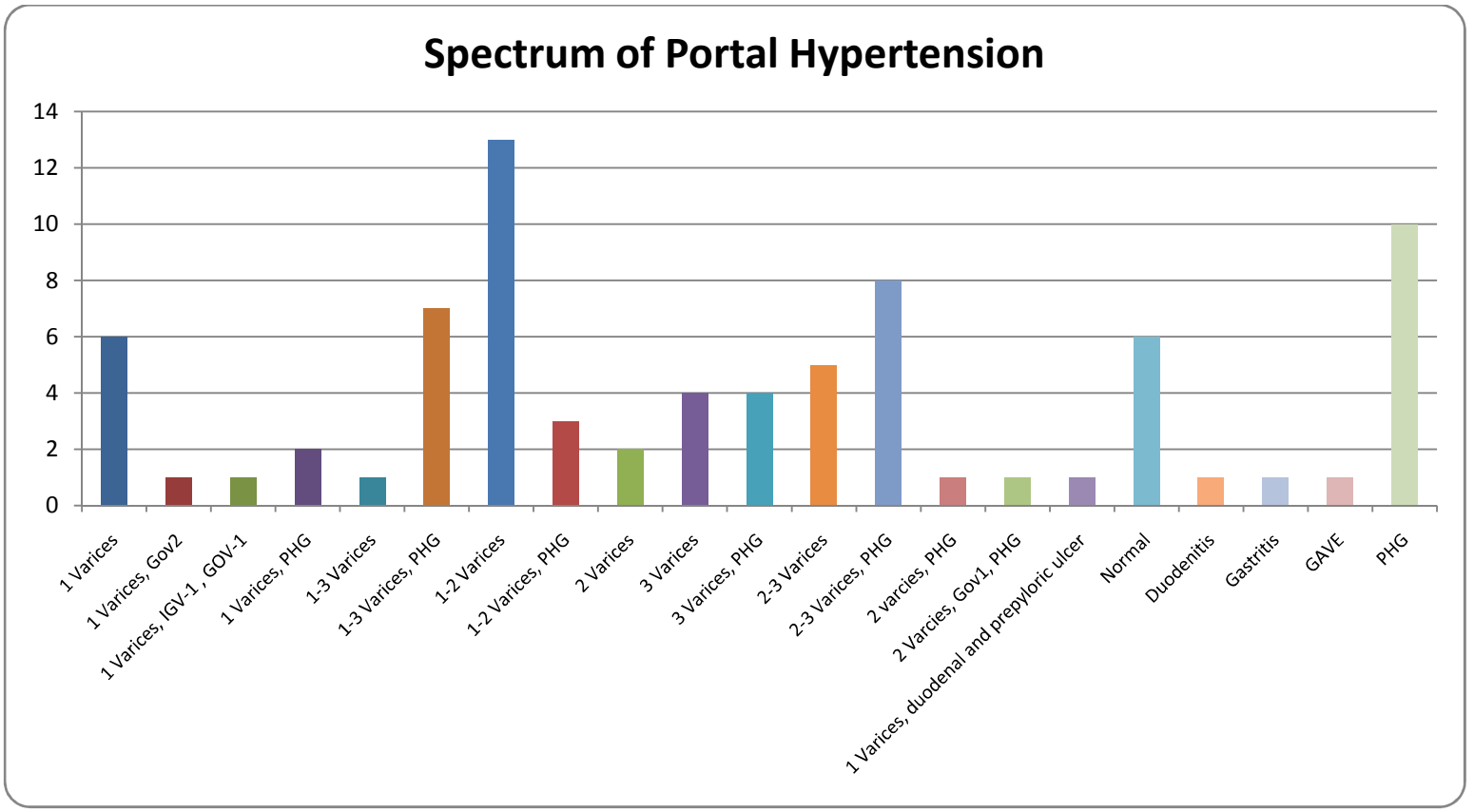


Figure 19: Severity of portal hypertension among NSBB and non NSBB patients

FREQUENCY OF THROMBOCYTOPENIA AMONG NSBB AND non NSBB PATIENTS

The mean platelet count in this study group was overall less (96000 cells /mm^3) than the normal (1.5 to 3.5 lakhs /mm^3), well correlating with the existing concept of 'lower the platelet count (<88,000) ,higher the portal pressure. So naturally, these patients were on non selective beta blockers (Fig 20/Table 7).

Table 7: Thrombocytopenia across both groups

Parameter	NSBB	Non NSBB	Overall
PLATELET (in Thousands) [§]	88(62.75-132.25)	110(61.25-180.75)	96(62-156.75)

N(%) are given in parenthesis; [¶]Mean ± SD; [§]Median (IQR)

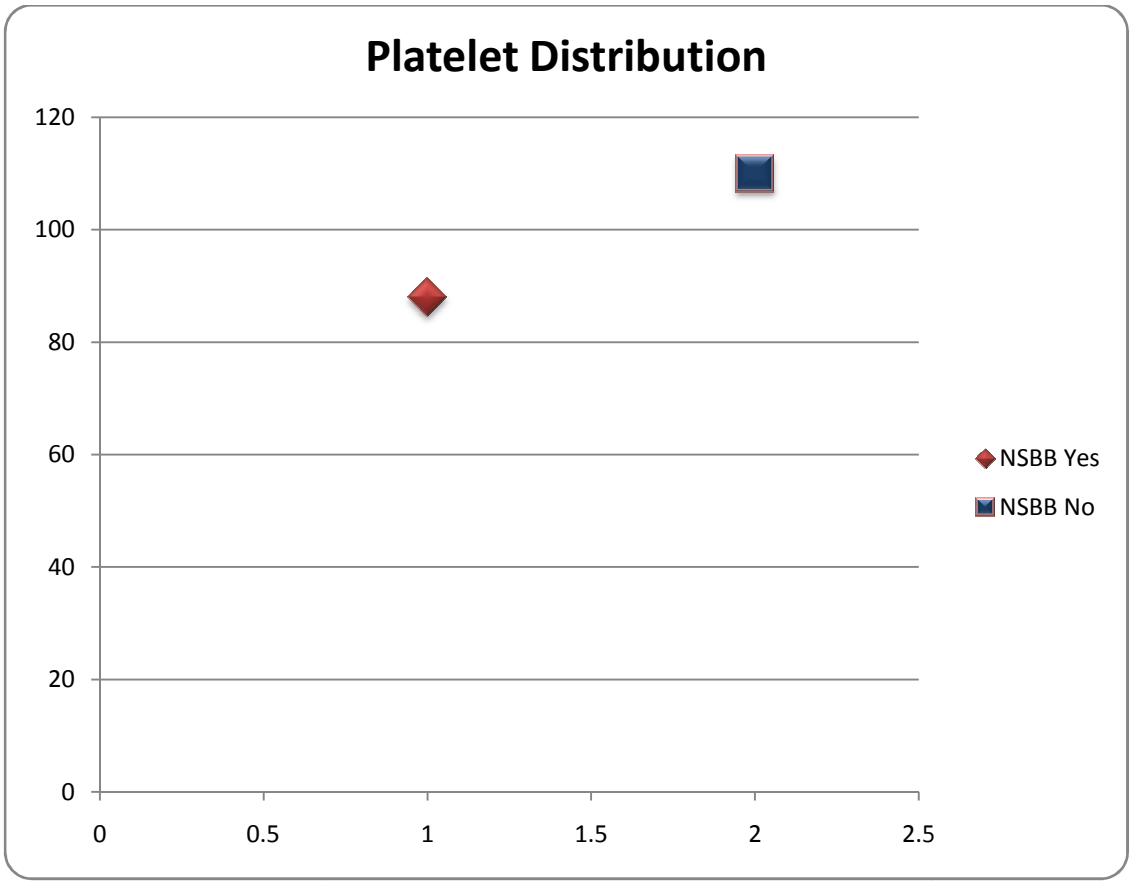


Figure 20: Platelet distribution

PATIENTS ON ANTIBIOTIC PROPHYLAXIS AGAINST SPONTANEOUS BACTERIAL PERITONITIS

34 patients (41.5%) were taking antibiotics for SBP prophylaxis of which 18 (52.9%) were in the NSBB and 16 (47.1%) were in the non -NSBB group.(Fig 21) In our hospital, we use Norfloxacin for the prevention of Spontaneous Bacterial Peritonitis. The antibiotic prophylaxis did not affect the outcomes , esp spontaneous bacterial peritonitis , because the p value was insignificant (p=0.913 (fig 21/Table 8).

Table 8: Antibiotic Prophylaxis in both groups

NORFLOX	BETA BLOCKER		TOTAL	P-VALUE
	YES	NO		
YES	18(40.9%)	16(42.1%)	34(41.5%)	
NO	26(59.1%)	22(57.9%)	48(58.5%)	
TOTAL	44	38	82	0.913

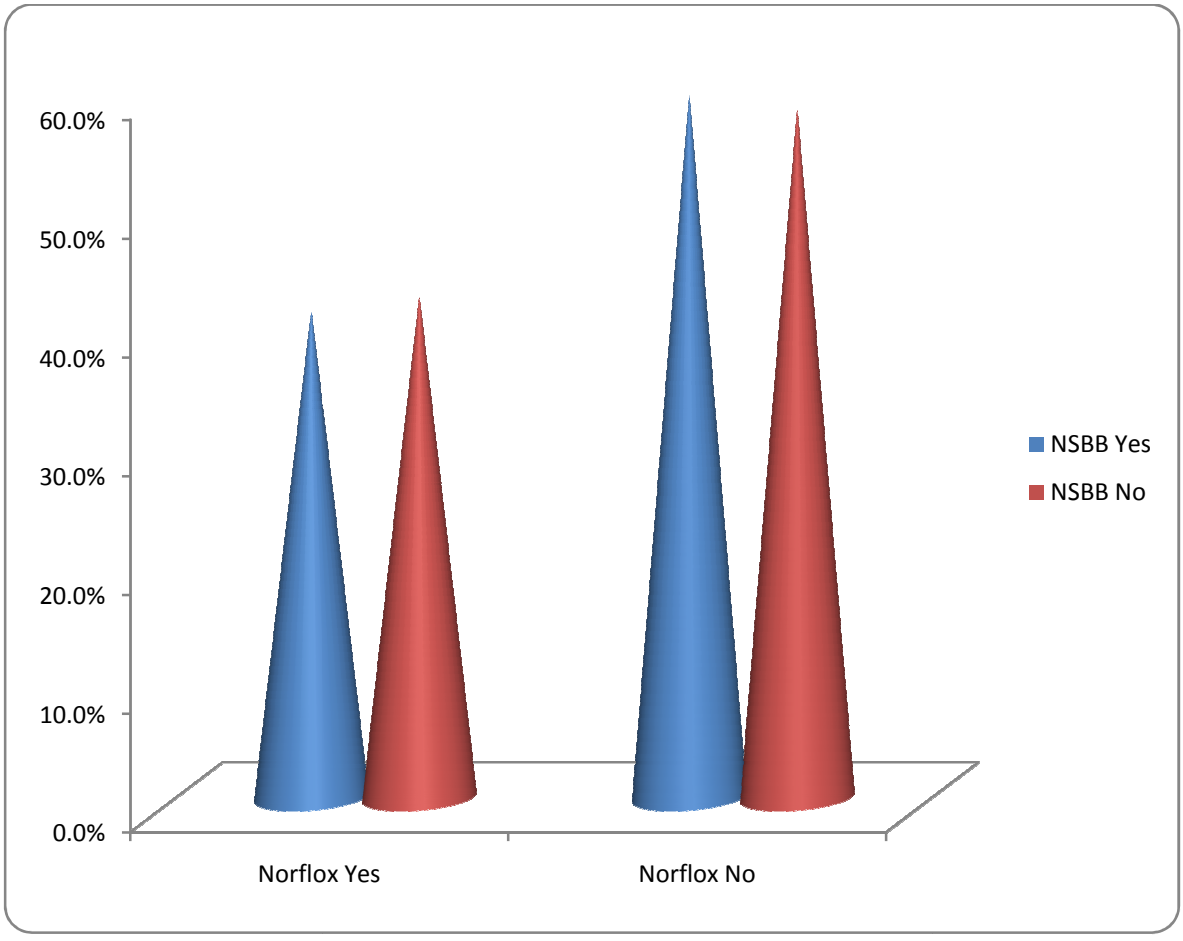


Figure 21: Antibiotic prophylaxis in both groups

Table 9: COMPARISON OF NSBB AND non-NSBB PATIENTS

PARAMETERS	BETA BLOCKER		OVERALL (N=82)
	YES (N=44)	NO (N=38)	
AGE (yrs)[¶]	48.41±9.29	47.34±7.32	47.91±8.41
SEX			
MALE	33(50.8%)	32(49.2%)	65
FEMALE	11(64.7%)	6(35.3%)	17
DURATION OF ILLNESS (yrs)[§]	2.0 (0.5-3.75)	1.0 (0.48-2.25)	1.5 (0.5-3.0)
MELD[§]	17(12-18)	16(12.5-18)	17(12-17)
UGI	24(68.6%)	11(31.4%)	35
PLATELET(in Thousands) [§]	88(62.75-132.25)	110(61.25-180.75)	96(62-156.75)
DIABETES	11(64.7%)	6(35.3%)	17
CIRRHOTIC CARDIOMYOPATHY	6(60%)	4(40%)	10
PVT	0(0%)	2(100%)	2
SBP PROPHYLAXIS	18(52.9%)	16(47.1%)	34
SBP	15(45.5%)	18(54.5%)	33
REFRACTORY ASCITES	6(54.5%)	5(45.5%)	11
HRS	2(25%)	6(75%)	8
HE	7(38.9%)	11(61.1%)	18

FREQUENCY OF SPONTANEOUS BACTERIAL PERITONITIS

33 patients (40.2%) were observed to have spontaneous bacterial peritonitis. 15 patients (45.5%) from the NSBB and 18 patients (54.5%) from the non NSBB group had developed spontaneous bacterial peritonitis at least once in their course of the illness (Table 10/Fig 22).

Table 10: Frequency of SBP in both groupss

SBP	NSBB	Non NSBB	Total
YES	15(45.5%)	18(54.5%)	33
NO	29(59.2%)	20(40.8%)	49

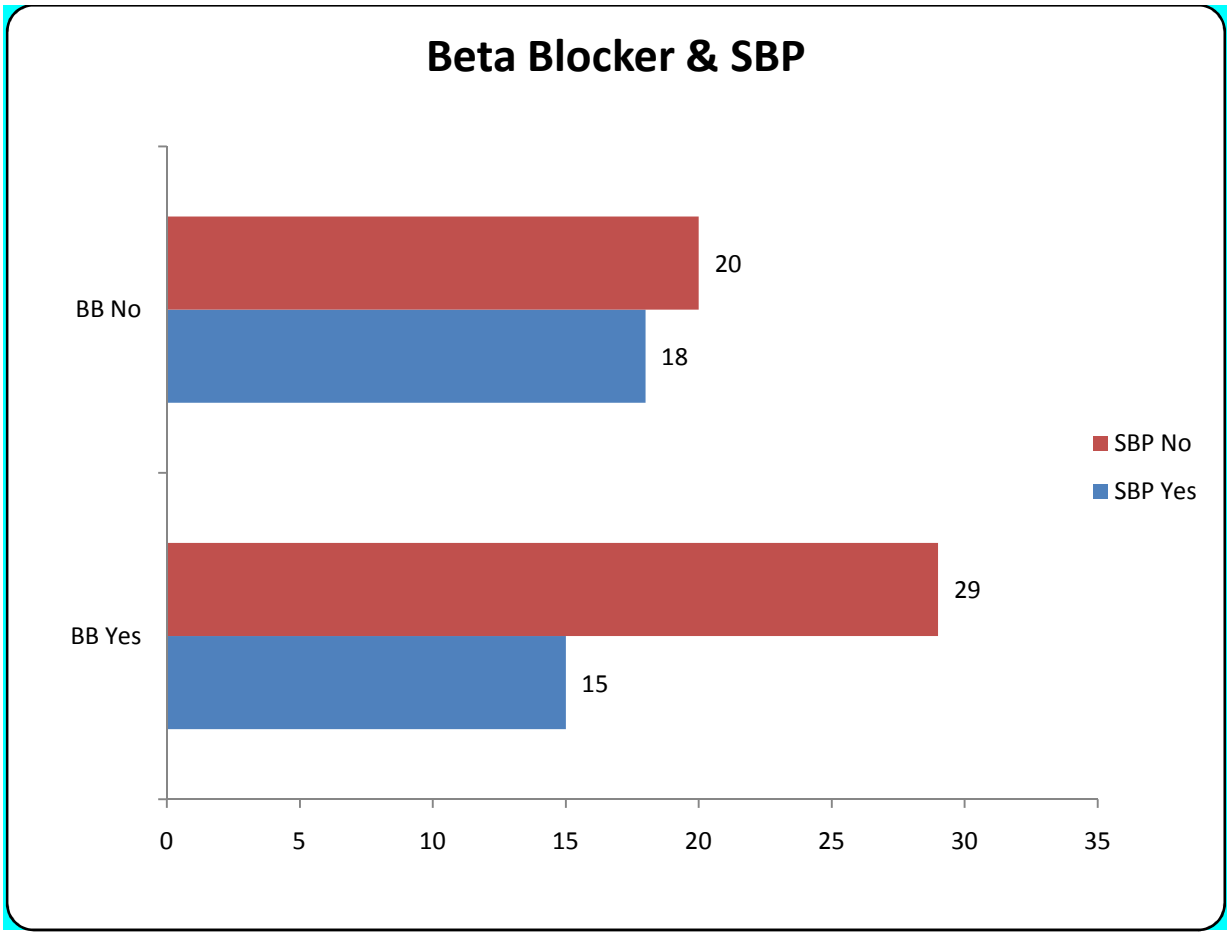


Figure 22: Frequency of spontaneous bacterial peritonitis

ASSOCIATION OF BETA BLOCKER THERAPY AND SPONTANEOUS BACTERIAL PERITONITIS

The association between use of beta blockers with spontaneous bacterial peritonitis was checked using chi-square analysis. And it is found that use of beta blockers is not a risk factor nor a protective one for spontaneous bacterial peritonitis(p=0.221) (table 11)

Table 11: Chi Square analysis for SBP

	Value	df	Asymp. Sig (2-Sided)	Exact Sig. (2-Sided)	Exact Sig. (1- Sided)
Pearson Chi-Square	1.495[a]	1	**0.221**	0.263	0.159
Continuity Correction[b]	0.994	1	0.319		
Likelihood Ratio	1.496	1	0.221	0.263	0.159
Fisher's Exact Test				0.263	0.159
Linear - by - Linear Association	1.477[c]	1	0.224	0.263	0.159
N of Valid Cases	82				

FREQUENCY OF REFRACTORY ASCITES

11 patients (13.4%) had refractory ascites. This comprised 6 patients (54.5%) from those on non selective beta blockers and 5 patients (45.5%) from the non - NSBB group (Table 12).

Table 12: Frequency of Refractory Ascites

REFRACTORY ASCITES	NSBB	Non NSBB	Total
YES	6(54.5%)	5(45.5%)	11
NO	38(53.5%)	33(46.5%)	71

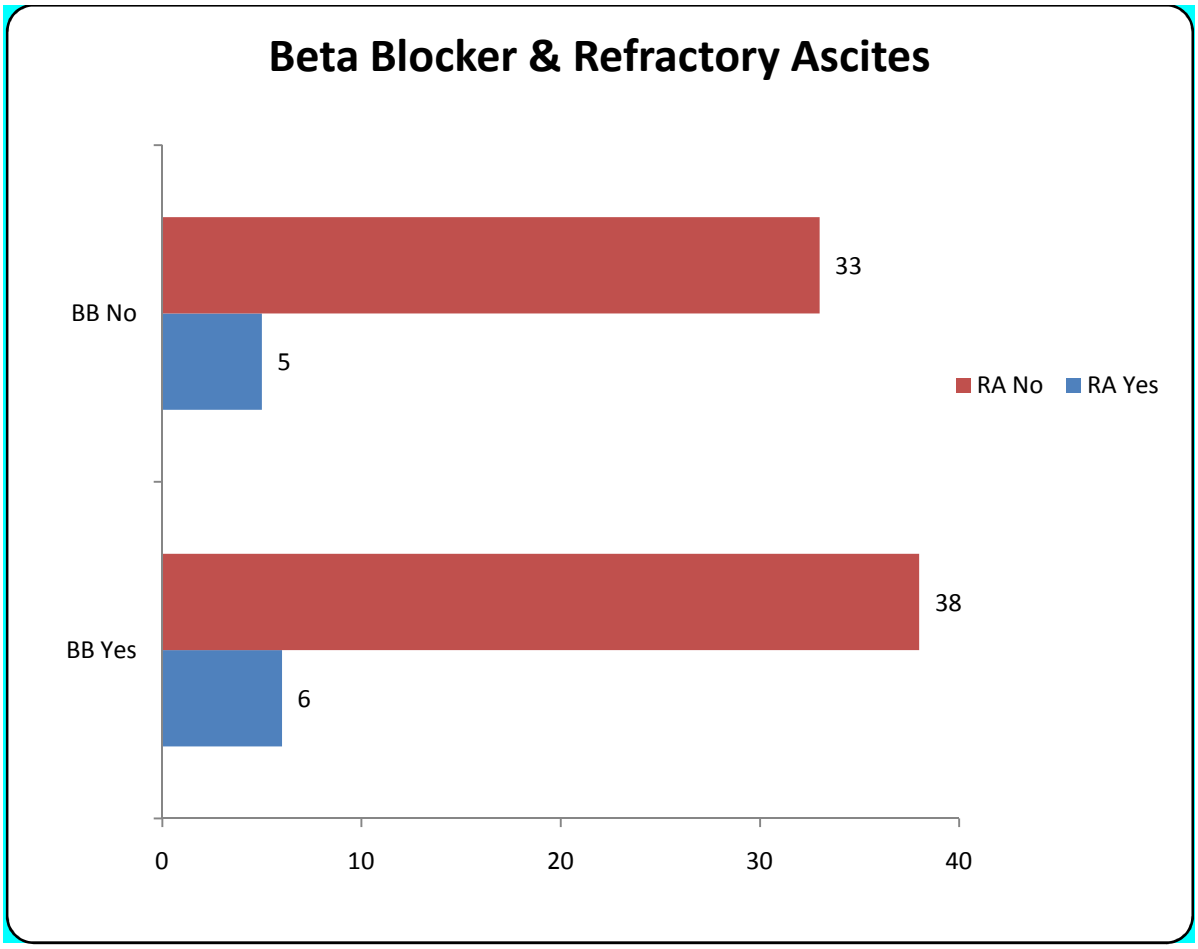


Figure 23: Frequency of Refractory Ascites

ASSOCIATION OF BETA BLOCKER THERAPY AND REFRACTORY ASCITES

Analysis of beta blocker and refractory ascites for aascoiation by Pearson Chi syuared analysis showed a asymptote significnce of 0.949 , which implies that there is no association between beta blockers and refractory ascites.

Table 13: Chi-square analysis for Refractory Ascites

	Value	df	Asymp. Sig (2-Sided)	Exact Sig. (2-Sided)	Exact Sig.(1-Sided)
Pearson Chi-Square	0.004[a]	1	**0.949**	1.000	0.605
Continuity Correction[b]	0	1	1.000		
Likelihood Ratio	0.004	1	0.949	1.000	0.605
Fisher's Exact Test				1.000	0.605
Linear - by - Linear Association	0.004[c]	1	0.950	1.000	0.605
N of Valid Cases	82				

FREQUENCY OF HEPATORENAL SYNDROME

Of this group only 8 patients (9.8%) had hepatorenal syndrome which was 2 (25%) from the NSBB and 6 (75%) from the non NSBB group (Table 14/Fig 24).

Table 14: Frequency of HRS

HRS	NSBB	Non NSBB	Total
YES	2(25%)	6(75%)	8
NO	42(56.8%)	32(43.2%)	74

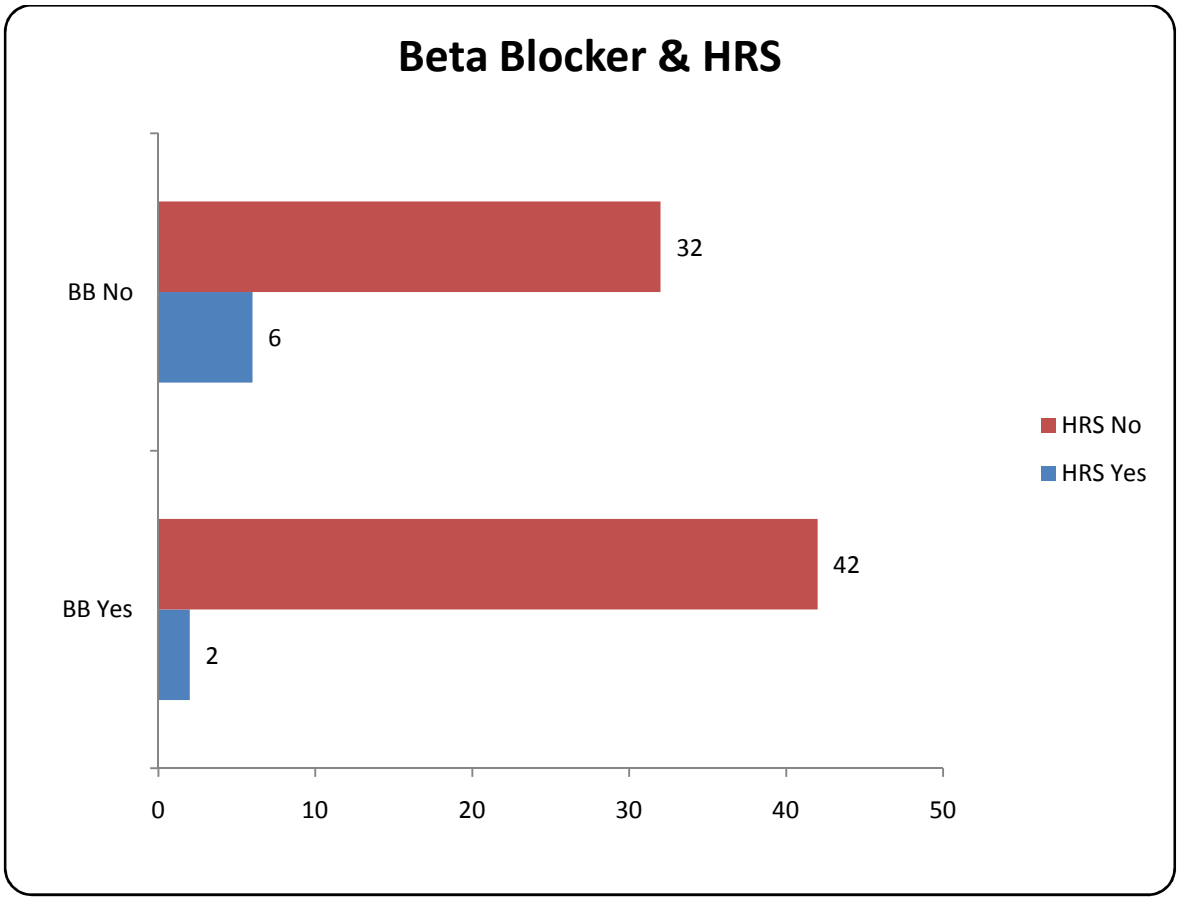


Figure 24: Frequency of HRS

ASSOCIATION OF BETA BLOCKER THERAPY AND HEPATO RENAL SYNDROME

In the Chi square analysis for hepatorenal syndrome and beta blocker use, the asymptote significance was 0.087. And the Fisher's Exact test was 0.136 (2 - sided). Thus, beta blockers have no role in the occurence of hepatorenal syndrome.

Table 15: Chi-square analysis for HRS

	Value	df	Asymp. Sig (2-Sided)	Exact Sig. (2-Sided)	Exact Sig. (1- Sided)
Pearson Chi-Square	2.928[a]	1	0.087	0.136	0.090
Continuity Correction[b]	1.79	1	0.181		
Likelihood Ratio	3.009	1	0.083	0.136	0.605
Fisher's Exact Test				0.136	0.605
Linear - by - Linear Association	2.892[c]	1	0.089	0.136	0.605
N of Valid Cases	82				

FREQUENCY OF HEPATIC ENCEPHALOPATHY

A total of 18 patients developed Hepatic encephalopathy at least once in their course of illness. Of these, 7 patients (38.9 %) belonged to the NSBB and 11 patients (61.1%) to the non NSBB group (Table 16/Fig 25).

Table 16: Frequency of HE

HE	NSBB	Non NSBB	Total
YES	7(38.9%)	11(61.1%)	18
NO	37(57.8%)	27(42.2%)	64

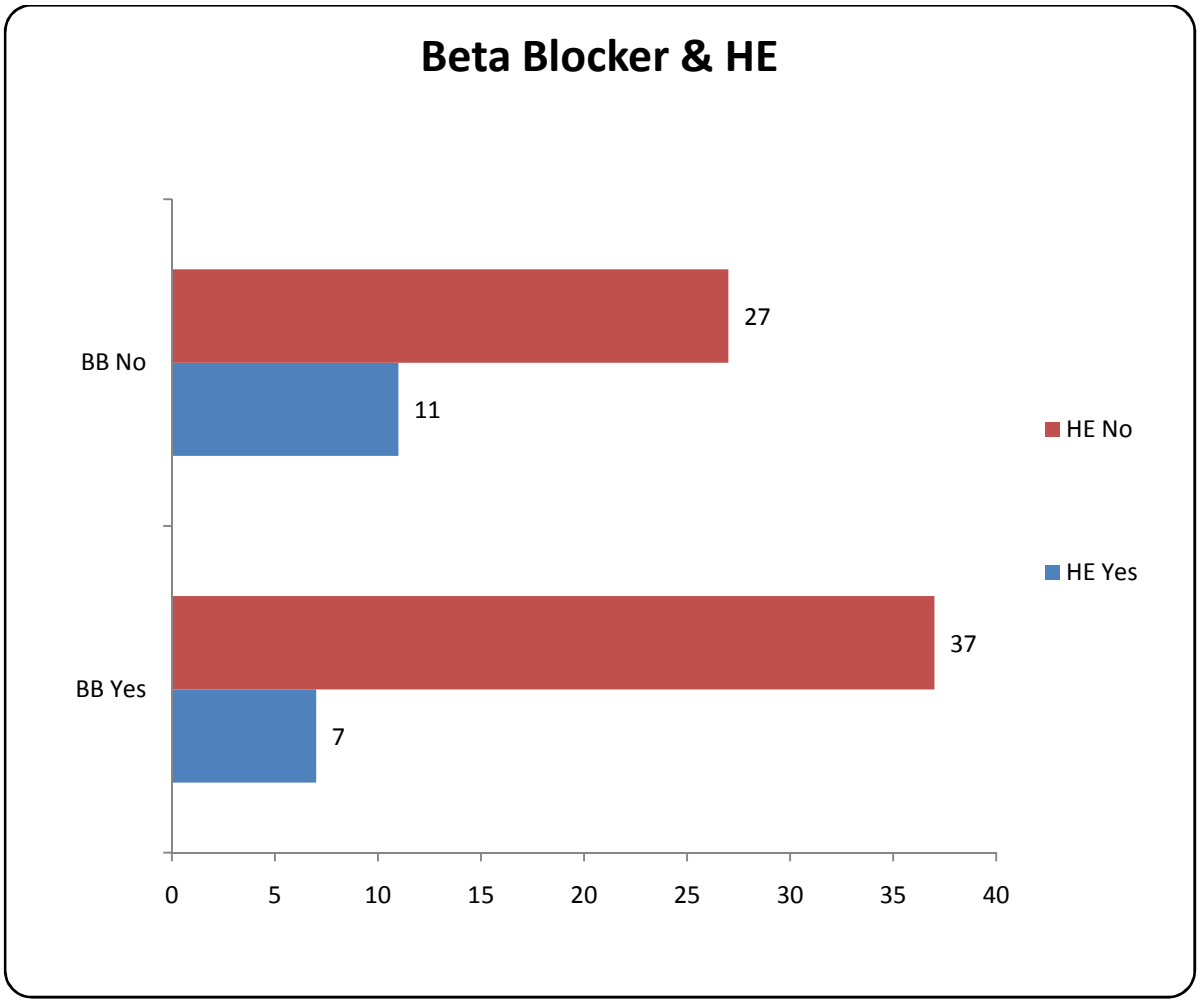


Figure 25: Frequency of HE

ASSOCIATION OF BETA BLOCKER THERAPY AND HEPATIC ENCEPHALOPATHY

In a chi-square analysis of hepatic encephalopathy against the use of beta blockers showed no significant association (asymptomatic significance = 0.155). The Fisher's Exact test showed an exact significance (2 sided) of 0.187. Once again, beta blockers neither protect from nor precipitate .hepatic encephalopathy .

Table 17: Chi-square analysis for HE

	Value	df	Asymp. Sig (2-Sided)	Exact Sig. (2-Sided)	Exact Sig.(1-Sided)
Pearson Chi-Square	2.023[a]	1	0.155	0.187	0.124
Continuity Correction[b]	1.334	1	0.248		
Likelihood Ratio	2.026	1	0.155	0.187	0.124
Fisher's Exact Test				0.187	0.124
Linear - by - Linear Association	1.999[c]	1	0.157	0.187	0.124
N of Valid Cases	82				

DISCUSSION

In this single centre, retrospective study we analyzed effects of non selective beta blocker therapy on the complications of cirrhosis in 82 patients.

As shown in this Chi - Square analyses, the p values were insignificant when the association of beta blockers were tested against hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis and refractory ascites.

As an added point of interest , we also looked at beta blockers if they could protect against cirrhotic cardiomyopathy being protective against cirrhotic cardiomyopathy as it would work against any cardiomypathy and cardiac failure (95). On the contrary, we did not find any such protective effect against the cardiac myocyte.

Also, beta blockers have been accused to be detrimental in the setting of End stage liver disease and especially those with Spontaneous Bacterial peritonitis where the predisposition to Hepatorenal syndrome is high. In this study, beta blockers use in those with advanced cirrhosis , as evident by their MELD did not affect the outcome of complications.

Again as an added interest, we wanted to see if beta blockers could also lead to portal vein thrombosis (96), Hypothetically, non selective beta blockers reduce the portal vein inflow and portal pressure and thereby lead to thrombosis in the lumen. But in this study, we did not any increased occurrence of portal vein thrombosis in patients taking beta blockers.

The dose of beta blockers used in our study was less when compared to the western data. All our patients had only received propranolol . The maximum dose

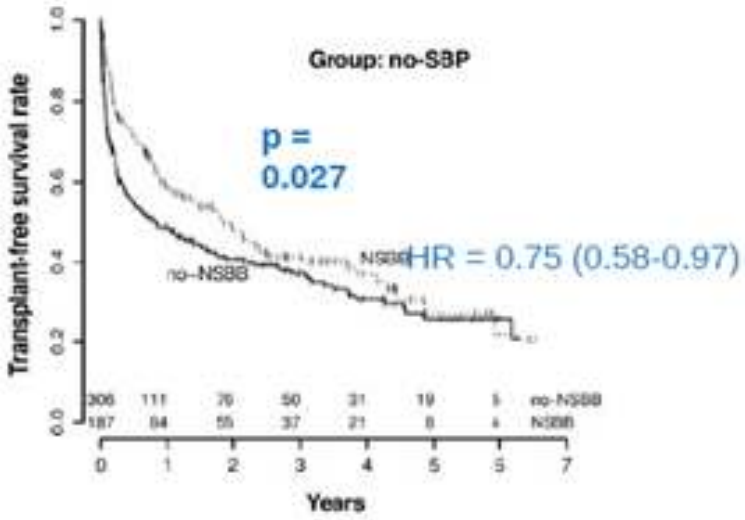
of propranolol used in this study was 120 mg /day, because of the unwanted side effects like bradycardia and hypotension. Still most patients tolerated the titration of beta blockers against their heart rates.

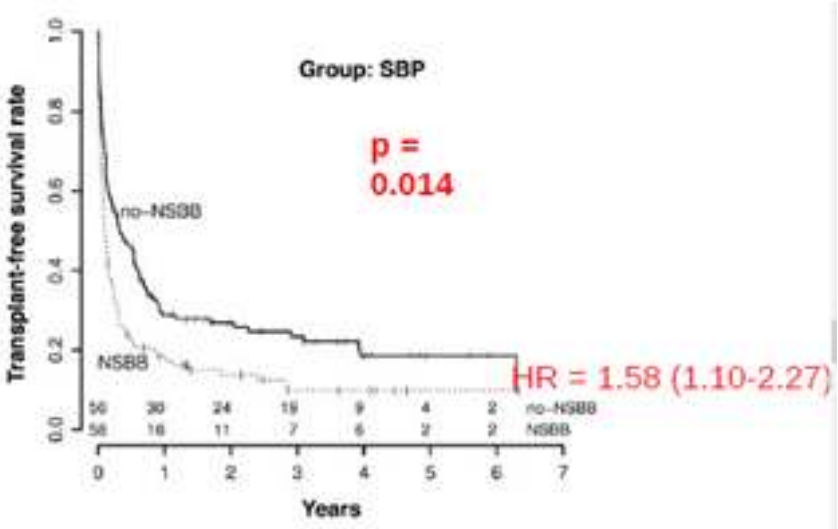
We also looked if diabetes , a predisposing factor for infection be a confounding factor . But diabetes incidence was also similar in both subgroups.

The early concerns of the safety of beta blockers stems from the Serste [4] et al who analyzed the impact of administering non selective beta blockers on the long-term survival in cirrhotics, with refractory ascites. The predominant cause of cirrhosis in both the NSBB and non NSBB group was ethanol, as in our study. Among the complications of our study, the frequency of hepatic encephalopathy and renal dysfunction were in line with the Serste study (p value for Hepatic encepahalopathy = 0.38, p value for renal dysfunction = 0.07), despite the Serste study having a higher mean MELD than our study patients.

Serste in his observational study had observed that in refractory ascites, mortality increases at one year by four times when beta blockers are used. Whether beta blockers contribute to refractoriness of ascites, in the first place remains unknown. In this study we found no association between beta blockers and refractory ascites.

On the contrary,Mandorfer et al [12] found an association between beta blockers and renal dysfunction in cirrhotics. But all these patients already had Spontaneous bacterial peritonitis which by itself can precipitate Hepatorenal syndrome irrespective of beta blockers usage.





Mandorfer et al. *Gastroenterology* 201

Figure 26: Transplant free survival in NSBB and non NSBB, Mandorfer et al

The same group also identified that beta blocker therapy did not affect the occurrence of Spontaneous bacterial peritonitis which is in line with our data.But patients who were not on beta blockers and did not have Spontaneous Bacterial peritonitis had a good transplant free survival compared to those who did not take beta blockers. Also these patients had fewer non elective hospitalizations (Fig 26). In this study, we did not have transplant patients which was a drawback and we could not anlayse if beta blockers impacted the transplant free survival chances.

In a study by Kimer et al [13], in 2014, they had retrospectively collected 61 patients with refractory ascites and looked for the complications of Hepato renal syndrome, Spontaneous Bacterial peritonitis, Hepatic encephalopathy, hospitalizations, bleeding frequencies and death in NSBB and non NSBB groups. Except for death, which we did not include in our study, the rest of the parameters were similar to the Kimer's study.

	No NSBB ($n = 38$)	NSBB ($n = 23$)	p-Value
Hepatic encephalopathy			
Patients with events	19	14	0.41
Total no of events	41	28	0.33
Hepatorenal syndrome			
Patients with events	12	10	0.33
Total no of events	17	11	0.56
Spontaneous bacterial peritonitis			
Patients with events	11	8	0.64
Total no of events	18	10	0.72
Bleeding from esophageal varices			
Patients with events	7	14	**0.0008**
Total no of events	11	25	**0.0021**
Hospitalizations			
Total	174	96	0.9759
Liver related	162	90	0.8562
Average per patient	4,26	4,17	0.8562
Death	26	15	0.7987

Table 18: Development of complications., Kimer et al.

A similar evidence comes from Poynard et al [14] who published a meta analysis in 1991 NEJM which included four randomized controlled studies that compared beta blockers and placebo in regards to bleeding, fatal bleeding and death. It was also observed in the study that ascites and beta blocker therapy may influence survival. Yet, the two factors were not linked in statistical analysis. Among these RCTs included, one RCT by Pascal et al [15]), where patients were stratified according to their Child Pugh score, the effect of non selective beta blocker on death rate was independent of severity of liver disease; on the corollary, beta blocker therapy did not affect the morbidity of cirrhotics even if they were Child

C. In our study group also we had Child C patient who did well with beta blockers.

In a Letters to the Editors to Hepatology 2011, Galbois et al wrote on retrospectively analyzing 68 patients admitted to ICU with cirrhosis and sepsis. They observed no difference in mortality between NSBB and non-NSBB-treated patients. Though we have not included ICU patients, NSBB were already having no impact in our patients with our ESLD patients.

In a similar kind of Letters to Editors to the same journal, in 2014, Robbins et al, [17] after analyzing one hundred and fourteen patients retrospectively who were undergoing regular abdominal paracentesis, they reported that there was no significant difference in survival between those taking NSBB versus those who did not. This is again in line with our study.

In another study comparing the effects of primary prophylaxis with beta blocker either alone or combined with endoscopic sclerotherapy vs no treatment, the PROVA study [18], a higher mortality was seen in the combined group. But the groups with beta blocker alone and no treatment had no significantly different mortality.

Aday et al,[19] did a retrospective study with a striking number of 2419 patients, with cirrhosis and portal hypertension. Patients were grouped as to having ascites only, varices only and having both. The outcome of interest was all cause -in hospital- mortality. It was concluded patients on beta blockers were less likely to die than those not on beta blockers. And this significant survival benefit was spread across all grades of ascites, even the most severe ones. This is in great

contradiction to the Serste study which was a case only study of 151 patients, when compared to this large numbered study.

Aligned with the previous study, Leithead et al, in Gut 2015, did a single centre observational retrospective study, taking patients with ascites who were listed for liver transplant and that beta blockers do not cause harm. Instead they are associated with decreased transplant-free mortality and reduced death during the waitlisted period. This again is an opposite conclusion of Serste study and a few others who did not support the use of beta blockers in advanced liver disease.

In a study by Qi X-S et al, [21] in World journal of gastroenterology 2014, it was suggested that beta blockers can lead to formation of thrombus in the portal vein. This was hypothesized due to the reduced cardiac output an splanchnic vasoconstriction that occurs in beta blocker therapy. These events can reduce portal venous blood flow velocity which eventually precipitates portal vein thrombosis.

But subsequently in a recent large longitudinal cohort analysis, [22] by Nery et al Hepatology 2015, they studied 1243 patients who did not have hepatocelluar carcinoma concluded that beta blocker therapy did not cause portal vein thrombosis. In our study also beta blocker therapy was not protective or a risk for portal vein thrombosis.

In those cirrhotics with End stage Liver Disease, immunological malfunctioning like altered phagocytic activity, hypocomplementemia, reduced bactericaidal and opsonic activity prevails which may all predispose to bacterial infections [58,64].

In Acute on Chronic Liver Failure, bacterial infections are a common causative factor. And non selective beta blockers have been demonstrated to improve survival at 1 month and at three months in Acute on chronic liver failure [65]. But these data were obtained from a post hoc analysis of the CANONIC cohort.

As obvious these results have been challenged by other researchers with an NSBB group experiencing a increased incidence of renal and cerebral failure despite a reduction in sepsis. But the overall in- hospital or 3 month outcomes were untouched by non selective beta blockers [66].

Also possible is endotoxaemia to occur more frequently in advanced liver disease, regardless of variceal status, which can exacerbate hyperdynamic circulation(67). As already discussed beta blocker mediated reduction of intestinal permeability and bacterial translocation may be partly independent of portal pressure reduction mechanisms.[62,68]

Chi - square analyses had shown no significant association between the uses of NSBB with any of these variables.

Beta blockers are said to reduce the incidence of spontaneous bacterial peritonitis by altering gut mucosal permeability. In our analyses, we did not find any protective effect of beta blockers against spontaneous bacterial peritonitis.

NSBB has also been found to increase the risk for hepatorenal syndrome, as quoted in the recent study by Mandorfer et al in 2014[6]. Again in our study population, we did not find any significant association between beta blockers use and the occurrence of hepatorenal syndrome.

Earlier, there were concerns about propranolol raising serum ammonia [7,8] and precipitating hepatic encephalopathy[9] in patients with cirrhosis. In our study, which was conducted in resource limited setting, serum ammonia levels could not be done. Still, our data and statistical analysis did not demonstrate significant association between beta blockers and the occurrence of overt or covert hepatic encephalopathy.

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CONCLUSIONS

In this study , no significant statistical association was found between the NSBB group versus the non NSBB group in terms of the following 4 complications of cirrhois:

1. Spontaneous Bacterial peritonitis

2. Refractory Ascites

3. Hepatorenal syndrome.

4. Hepatic encephalopathy.

To conclude, in this study non selective beta blockers are neither protective nor a risk factor for spontaneous bacterial peritonitis, refractory ascites, hepatorenal and hepatic encephalopathy.

And therefore, we suggest that beta blockers can be continued safely in cirrhotics

LIMITATIONS

1. Retrospective study

2. Small sample size

3. Serum ammonia not measured in patients with hepatic encephalopathy.

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PROFORMA

Name : Age: Sex: DDHD no:

Duration of illness: Etiology of cirrhosis: No of hospital admissions:

Comorbid illness:

Medications:

Beta blockers : yes/ no

MELD score: CTP Score: DF:

Previous history of GI bleed and therapy :

Presence of HRS:

Presence of Hepatic Encephalopathy:

Presence of Refractory Ascites:

Presence of Spontaneous bacterial peritonitis:

INVESTIGATIONS

Bili total		Hb%		HBsAg		USG abdomen
Bili direct		TC		Anti-HCV		
SGOT		DC		HIV		
SGPT		Platelets		PT/INR		
SAP		Urine alb		MHE		Portal Doppler
Tot prot		RBS		ECG		
S.alb		Bl.urea		Echo		
S.glob		S.creat				

Esophago gastroduodenoscopy:

Presence of varices: Grading :

Ascitic fluid analysis:

TC DC Protein Albumin SAAG Cytology

Culture and sensitivity

Master Data

Name	Age	Sex	Duration Of Illness	Etiology	UGI Bleed	Admissions	MELD	CTP	SAP	Platelet Count
Palani	45	Male	2 yrs	Ethanol	1	16	13	b	247	72000
Periyanayagam	60	Male	3 month	Ethanol/HBV	0	2	17	b	144	66000
Sampath	53	Male	16 years	HBV	0	5			146	52000
Madhavan	54	Male	1 year	Ethanol	0	2	16	8b	343	123000
Ramadoss	47	Male	6 months	Ethanol	0	5	15	12c	192	42000
Valli	34	Female	4 years	HBV	1	2			214	49000
Sallaikannan	43	Male	6 months	Ethanol/HBV	0	5			245	91000
Murugan	40	Male	6 months	Ethanol	1	2	18	10c	353	30000
Krishnamoorthy	70	Male	2 years	Ethanol	0	7	16	12c	46	65000
Mannammal	60	Female	5 years	Ethanol	1	4			231	80000
Velmurugan	44	Male	1 year	Ethanol	1	4	18	9b	428	41000
Dekesnamoorthy	55	Male	2 years	Ethanol	1	4			100	100000
Ramanaathan	33	Male	4 months	Ethanol	1	1	17	10c	305	41000
Madhavamahendran	57	Male	7 years	HBV	1	3			179	68000
Arumugam	40	Male	5 months	Ethanol	0	1			442	
Balakrishnan	40	Male	3 years	Ethanol	2	1	17	9b	284	133000
Ravi	49	Male	3 months	Ethanol	0	1			311	180000
Babu	40	Male	1 year	Ethanol	0	3			415	41000
Ramu	42	Male	1 year	Cryptogenic	0	0			120	120000
Pounnuammal	55	Female	3 months	Cryptogenic	0	1			410	109000
Suburamani	56	Male	18 months	Ethanol	1	1	18	9b	261	164000
Pasupathi	44	Male	18 months	Ethanol	0	1			311	100000
Rameja	48	Female	3 months	NASH	0	3	8	9b	219	189000
Kayatharu	49	Male	3 months	Cryptogenic	0	0			320	
Vijayalakshmi	44	Female	1 month	NASH	0	0			184	58000
Dhanam	45	Female	5 years	EHPVO/hcv	0	0			48	189000
Amaravathi	40	Female	8 years	NASH	0	5	18	7d	200	33000
Venketashan	42	Male	8 months	Ethanol	1	1	11	9b	228	45000
Sathyaraj	64	Male	1 year	Ethanol			7	6a	142	61000
Vijayalakshmi	65	Female	6 years	Cryptogenic	1	1			88	180000
Karunakaran	45	Male	6 years	Ethanol	1	4			187	88000
Arunachalam	50	Male	5 years	Ethanol	1	3			140	75000
Kanniyappan	54	Male	3 months	Ethanol	0	1	22	11c	384	181000
Baskar	48	Male	6 months	Ethanol	1	2			274	
Baskaran	38	Male	2 years	Ethanol	1	2	17	10c	497	190000
Durai	50	Male	2 months	Ethanol	1	0	12	10c	752	82000

Ramesh	41	Male	6 months	Ethanol	0	3	14	9c	531	62000
Baskaran	57	Male	6 months	Ethanol	0	2	23	10c	313	56000
Gopinath	35	Male	1 year	ethanol	0	6	22	11c	269	180000
Devaraj	33	Male	2 years	Ethanol	0	2			94	19200
Muniyandi	52	Male	1 Month	Ethanol	0	1	13	8b	298	208000
Koteeswaran	49	Male	5 years	Ethanol	0	5	28	13c	275	100000
Devarajan	41	Male	5 months	Ethanol	0	0	18	10c	125	93000
Vijayakumari	58	Female	18 months	NASH	0	2	23	8b	749	103000
Hariharan	60	Male	4 years	Ethanol	2	3	16	10c	219	130000
Sam	44	Male	4 years	Ethanol	0	1	24	11c	379	93000
Kalavathy	50	Female	2 years	HBV	0	2	9	5a	92	140000
Dhayalan	47	Male	2 years	Ethanol	0	1	18	9b	235	116000
Ravi Kumar 44	44	Male	6 months	Ethanol	0	2			438	204000
Murugan	40	Male	1 year	Ethanol	1	2	18	10c	285	30000
Palani	45	Male	2 years	Ethanol	0	2			287	21000
Veera Ragavan	57	Male	1 year	Cryptogenic	1	2	17	11c	493	62000
Vimala	35	Female	3 months	Cryptogenic	1	1	12	9b	154	43000
Poongavanam	61	Male	3 months	Ethanol	0	1	11	8b	366	180000
Devasagayam	47	Male	2 months	Cryptogenic	0	0			75	83000
Palani	42	Male	3 years	Ethanol	0	2	19	11c	147	157000
Ravi Chandran	45	Male	6 years	Ethanol	1	4			125	156000
Manoharan	60	Male	3 years	Ethanol	3	0			101	
Malathy	59	Female	2 years	NASH	0	1	14	9b	229	310000
Subburathinammal	40	Female	3 years	Autoimmune	2	2	14	8b	231	56000
Jayakumar	39	Male	6 months	Ethanol/HBV	1	1	10	8b	211	160000
Jaishankar	50	Male	6 months	Ethanol	1	1	11	7b	227	111000
Sasikumar	38	Male	8 months	Ethanol/HBV	1	1	20	11c	303	44000
Chellamuthu	60	Male	9 months	Ethanol	0	1			140	
Ravi	54	Male	9 months	Ethanol	0	0			129	
Sivakumar	35	Male	2 years	Ethanol	1	5	26	13c	292	88000
Bishma Rao	48	Male	12 months	Ethanol	2	1	17	9b	431	250000
Hameedha Begam	55	Female	3 years	HCV	4	4	6	5a	154	80000
Santhanam	51	Male	4 years	Ethanol	0	0			274	99000
Ezhumalai	53	Male	3 years	HBV	3	4	14	8b	158	66000
Jeyakumar	45	Male	2 years	Ethanol	0	4	18	9c	185	88000
Sudha	38	Female	3 months	Cryptogenic	0	0	12	8b	182	74000
Chokkalingam	57	Male	6 years	Ethanol	0	0	11	9b	81	206000
Devarajan	41	Male	6 months	Ethanol	0	0	17	11 c	133	93000
Govindharaj	58	Male	5 years	Ethanol	2	3	17	11c	110	120000
Rani	55	Female	3 years	Ethanol	0	2	12	8b	105	150000

Govindharaj	38	Male	4 yeas	Ethanol	1	3	11	8b	176	106000
Ramachandran	45	Male	2 years	Ethanol	0	2	13	9b	106	342000
Lakshmi	56	Female	6 years	NASH	3	2	12	7b	331	149000
Anbarasu	38	Male	2 years	Ethanol	0	3	18	10c	251	120000
Uthirapthy	42	Male	2 years	Ethanol	1	3	17	10c	187	260000
Ravi	48	Male	3 years	Ethanol	0	10	18	11c	223	260000

Name	Diabetes	Cirrh Cardio	PVT	Beta Blocker	Norflox	SBP	Refractory Ascites	HRS	HE	VOGD
Palani	No			No	no	2	12	2	2	Normal
Periyanayagam	No		no	Yes	no		0	0	0	2-3 Varices
Sampath	No		yes	No	no		0	0	0	1-2 Varices
Madhavan	No		no	No	yes	1	0	0	0	PHG
Ramadoss	Yes	no	no	No	yes	4	5	1	2	PHG
Valli	No	no		No	no		0	0	0	1-2 Varices
Sallaikannan	No			Yes	yes	4	4	0	0	1-3 Varices, PHG
Murugan	No	no	no	Yes	no		0	0	0	1-2 Varices
Krishnamoorthy	No	yes		Yes	no	3	5	0	0	3 Varices
Mannammal	No	no	no	No	yes	1	0	0	1	Normal
Velmurugan	No			No	no	3	0	1	2	2 Varices
Dekesnamoorthy	Yes			Yes	no	1	0	0	0	2-3 Varices, PHG
Ramanaathan	No			Yes	no		0	0	0	1 Varices, Gov2
Madhavamahendran	No			Yes	no		0	0	0	1-3 Varices, PHG
Arumugam	No	yes		No	yes	1	0	0	0	PHG
Balakrishnan	No			Yes	no		0	0	0	2-3 Varices, PHG
Ravi	No	no		No	no		0	0	0	Normal
Babu	No			Yes	yes	1	0	0	1	1-2 Varices
Ramu	No	no	no	No	no		0	0	0	1-2 Varices
Pounnuammal	Yes		no	No	no	1	0	0	0	Normal
Suburamani	No	yes		No	no	1	0	0	0	1-2 Varices
Pasupathi	No			Yes	no		0	0	0	2-3 Varices, PHG
Rameja	Yes			No	yes	1	0	0	2	1-2 Varices, PHG
Kayatharu	No			Yes	no		0	0	0	1-2 Varices, PHG
Vijayalakshmi	Yes	no	no	No	no		0	0	0	2 Varices
Dhanam	No		no	Yes	no		0	0	0	1-3 Varices, PHG
Amaravathi	Yes			Yes	no	3	2	0	3	2-3 Varices, PHG
Venketashan	No		no	No	no		0	0	0	3 Varices
Sathyaraj	Yes	no	no	No	no		0	0	0	
Vijayalakshmi	No			Yes	no		0	0	0	3 Varices

Karunakaran	No			Yes	no	2	0	0	0	1-3 Varices, PHG
Arunachalam	Yes			Yes	yes		0	0	1	2-3 Varices
Kanniyappan	No	yes	no	No	yes		0	0	0	1 Varices
Baskar	Yes			Yes	no		0	0	0	2-3 Varices, PHG
Baskaran	Yes	no		Yes	yes		0	1	0	2 Varcies, Gov1, PHG
Durai	No	no	no	No	no		0	0	0	Normal
Ramesh	No			No	yes	2	0	0	1	1 Varices
Baskaran	Yes	no	no	Yes	no	1	1	0	1	2 varcies, PHG
Gopinath	No	no	no	No	yes	4	2	1	2	1-2 Varices
Devaraj	No		no	Yes	no		0	0	0	2-3 Varices
Muniyandi	No			No	no		0	0	0	1 Varices
Koteeswaran	No			Yes	yes	3	3	0	1	1-3 Varices, PHG
Devarajan	No			No	no		0	0	0	PHG
Vijayakumari	Yes		no	Yes	yes		0	0	0	PHG
Hariharan	No			Yes	yes		0	0	1	1 Varices, IGV-1 , GOV-1
Sam	No			No	no		0	0	0	PHG
Kalavathy	No			Yes	no		0	0	0	1-3 Varices
Dhayalan	No	yes	no	Yes	yes		0	1	0	1-2 Varices
Ravi Kumar 44	No		no	No	yes	1	1	0	0	1 Varices, PHG
Murugan	No	no	no	Yes	yes		0	0	0	1-2 Varices
Palani	No	no		No	no		0	0	0	Normal
Veera Ragavan	No	yes	no	Yes	no		0	0	0	1-3 Varices, PHG
Vimala	No		no	Yes	no		0	0	0	1-3 Varices, PHG
Poongavanam	No		no	Yes	yes		0	0	0	2-3 Varices, PHG
Devasagayam	Yes	no		Yes	yes		0	0	0	1-2 Varices
Palani	No	no	no	No	yes		0	0	1	PHG
Ravi Chandran	No	no		No	no	1	0	1	3	Gastritis
Manoharan	No	no		Yes	yes	1	0	0	1	1-2 Varices, PHG
Malathy	Yes	no	no	No	no		0	0	0	GAVE
Subburathinamm al	No	no		Yes	no		0	0	0	2-3 Varices, PHG
Jayakumar	No	no		Yes	yes	1	0	0	0	1 Varices, duodenal and prepyloric ulcer
Jaishankar	No	yes	no	No	no	1	0	0	0	PHG
Sasikumar	No			No	yes		0	0		1 Varices
Chellamuthu	No		yes	No	no		0	0	0	Duodenitis
Ravi	No			Yes	yes		0	0	0	1-2 Varices
Sivakumar	No	yes	no	Yes	no	2	5	0	0	1 Varices, PHG
Bishma Rao	No	no	no	Yes	no		0	0	0	2-3 Varices, PHG
Hameedha Begam	No	no	no	Yes	no		0	0	0	3 Varices, PHG
Santhanam	No	no		No	yes		0	0	0	1 Varices
Ezhumalai	Yes	no	no	Yes	no		0	0	0	3 Varices, PHG

Jeyakumar	Yes	no	no	Yes	yes	1	0	0	0	1-2 Varices
Sudha	No	no	no	Yes	no		0	0	0	2-3 Varices
Chokkalingam	No	no	no	No	no		0	0	0	1-2 Varices
Devarajan	No	no	no	No	yes		0	0	0	PHG
Govindharaj	No	yes	no	Yes	yes	2	0	0	0	3 Varices, PHG
Rani	No	yes	no	Yes	no		0	0	0	3 Varices, PHG
Govindharaj	No	no	no	Yes	yes	1	0	0	0	3 Varices
Ramachandran	No	no	no	No	yes	1	0	0	1	1 Varices
Lakshmi	Yes		no	Yes	yes	1	0	0	0	2-3 Varices
Anbarasu	No	no	no	No	yes	1	0	0	0	
Uthirapthy	No	no	no	No	no	1	0	0	0	
Ravi	No	no	no	No	yes	7	5	2	2	PHG

INSTITUTIONAL ETHICS COMMITTEE
GOVT. KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No.23/2017 Meeting held on 17.04.2017

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval **"Influence of Beta blockers on complication of Cirrhosis"** submitted by Dr.Kayalvizhi Rajini, D.M. (Medical Gastroenterology), PG Student, GKMC, Chennai-10

The Proposal is APPROVED

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

DEAN
Govt. Kilpauk Medical College,
Chennai-10.